Predictors of psychosocial outcomes in women with early stage breast cancer

den Oudsten, B.L.

Publication date:
2009

Document Version
Publisher's PDF, also known as Version of record

PREDICTORS OF PSYCHOSOCIAL OUTCOMES IN WOMEN WITH EARLY STAGE BREAST CANCER

Predictors of psychosocial outcomes in women with early stage breast cancer

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit van Tilburg,
op gezag van de rector magnificus, prof. dr. Ph. Eijlander,
in het openbaar te verdedigen ten overstaan van een door het
college voor promoties aangewezen commissie
in de aula van de Universiteit op vrijdag 29 mei 2009 om 14.15 uur

door

Brenda Leontine den Oudsten

geboren op 4 januari 1979 te Gouda

Promotores:	Prof. dr. G.L. van Heck
	Prof. dr. J.A. Roukema
	Prof. dr. J. de Vries
Promotiecommissie:	Prof. dr. J.K.L. Denollet
	Prof. dr. J.C.J.M. de Haes
	Prof. dr. M.F. von Meyenfeldt
	Prof. dr. R. Sanderman
	Dr. A.F.W. van der Steeg

ISBB/EAN: 978-90-5335-187-1

Printed by Ridderprint Offsetdrukkerij B.V., Ridderkerk

Contents

Chapter 1
General introduction and outline of the thesis

Breast cancer incidence and prevalence

In 2006, there were an estimated 3,191,600 new diagnoses of cancer in Europe. Breast cancer (BC) is currently the most common form of malignancy in women. In the Netherlands, 11% of all women will develop BC during their life span [1]. Moreover, BC is the leading cause of death in women [2].

Increasing age is a major risk factor for BC. In addition, higher socioeconomic status, a family history of BC, early menarche, late menopause, lengthy exposure to postmenopausal estrogens, childlessness, and first childbirth at late age are also associated with an increased risk of BC [3].

Partly due to advances in early detection (BC screening) and medical treatment (new adjuvant systemic and/or hormone therapies), women with BC will have an increased chance to survive for a longer period of time [4]. As survival time increases, the group of BC survivors is gradually growing. Therefore, it becomes important to address the impact of BC and its treatment on long-term psychosocial outcomes. Before describing any of the psychosocial outcomes found in the literature, an overview will be provided on breast cancer treatment.

Breast cancer treatment

Most women in developed countries diagnosed with early stage BC will have surgical treatment [5]. In recent decades, treatment for BC has become more complex. Breast conserving therapy (BCT) has become an alternative to mastectomy (MTC) in early stage BC due to its potential for better cosmetic results and its equivalent survival rate compared with mastectomy [6, 7]. Both surgical treatments may be chosen, when BC is diagnosed in an early stage (i.e., the tumour is smaller than 5 cm in diameter and there are no apparent metastases). When BCT is performed, the tumour is removed with a rim of surrounding healthy breast tissue followed by radiation therapy to the rest of the breast. MTC involves complete removal of all breast tissue including the nipple. As part of this surgical treatment, in most patients the lymph nodes in the axilla are staged, preferably with the sentinel node procedure, which is an invasive method to identify the lymph node that is the indicator for node metastases in the axilla. If the sentinel lymph node appears to contain cancerous cells, a complementary lymph node dissection is performed during a second operation. In some cases

axillary lymph node dissection is performed without preceding sentinel node procedure [8].

Dependent on tumour size, degree of differentiation of the tumour, and the presence of axillary metastases, adjuvant treatment (chemotherapy, hormone therapy, radiotherapy) is recommended. Each type of adjuvant therapy can be used separately or in combination across time.

General quality of life

Quality of life (QOL) has been established as a primary endpoint in cancer medicine in recent years [9, 10]. The number of studies assessing QOL in BC has increased enormously.

There is debate on how to conceptualize QOL. If one adopts a critical approach, then, a large number of the published studies actually have not assessed QOL, but have measured related concepts, such as health status (HS) and/or health-related quality of life (HRQOL) [11]. HS, HRQOL, and QOL are often considered interchangeable, but these concepts are not the same [11, 12]. In general, it is accepted that QOL is multi-dimensional consisting of at least three broad domains: physical, psychological, and social (well-being). QOL is conceptualized by the World Health Organization Quality of Life group (WHOQOL Group) as 'an individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards and concerns. It is a broad-ranging concept incorporating in a complex way the person's physical health, psychological state, level of independence, social relationships, personal beliefs and relationship to salient features of the environment' (p. 1405) [13]. As a consequence, QOL is subjective, and, therefore, can, strictly speaking, only be judged by individuals themselves. Both HS and HRQOL focus more exclusively on health aspects. HRQOL is measured when research is focusing on satisfaction within health-related domains, such as physical well-being, psychological well-being, and social relationships [12]. Thus, HRQOL is QOL but restricted to the perception of functioning. In general, HS instruments assess the impact of disease on health-related functioning [14]. Patients are asked about their physical possibilities, state of mind, and social activities. Thus, HS instruments do not contain questions about the persons' feelings concerning their functioning.

When the above-mentioned perspective is taken into consideration, then we conclude that until now in oncology most studies have focused on HS, even when the employed assessment instruments are labelled as HRQOL-scales or QOL-scales. More specifically stated: most studies have examined potential differences in HS between surgical options or identifying factors associated with HS. In general, findings have indicated that HS is better after BCT than MTC [15-19].

In the first part of this thesis, we will focus on overall QOL. In the remaining parts, the focus is on two domains of QOL: the psychological domain and the social domain. In the next paragraph, the literature on psychosocial outcomes in early stage BC will be summarized.

Psychosocial outcomes

Being diagnosed with BC and living with BC are stressful experiences that may have a serious impact on multiple aspects of patient's daily life [20]. Several studies have found that the majority of women diagnosed with BC cope quite well psychosocially, for instance, with reports of renewed vigour for life or stronger interpersonal relationships [21, 22]. However, negative consequences in functioning have also been found frequently.

Psychosocial research in the field of early stage BC has at least two important uses [23]. First, it can be employed to identify subgroups of patients at (greatest) risk of psychological morbidity. Second, it may provide information to guide women in making choices, for instance, to select the treatment that is least likely to adversely affect those aspects of well-being that are most important for them [23].

Depressive symptoms

The emotional consequences of BC have received much attention in the scientific literature, especially with regard to depression. In spite of better prospects, receiving a BC cancer diagnosis is still very stressful. Taking this into account, it is quite conceivable that BC patients have a high risk of developing mood disorders [24]. The prevalence of depression or depressive symptoms ranges from 1.5% to 50%, depending on the study population, the definition of depression, and the assessment instruments used [25]. The majority of studies have found that

20% to 30% of the women experience elevated depressive symptoms, although the prevalence of major depressive disorder may be considerably lower [25, 26]. Depressive symptoms are probably highest in the first 6 months after cancer diagnosis and will thereafter decline over time [27].

The presence of depressive symptoms has a detrimental impact on QOL [28]. Furthermore, it is associated with poorer compliance [29, 30], which, in turn, may affect disease outcome, increased morbidity, and possibly mortality [31]. However, the factors associated with the presence of depressive symptoms are still not clearly understood. There are several reasons for this state of affairs. First, few studies have examined women with early stage BC *prospectively*. In addition, the majority of the studies that examine, predictors of depressive symptoms do not take into account a broad spectrum of factors, i.e., sociodemographic, clinical, and psychological. As a consequence, this is an important target area for research and clinical practice.

A number of factors influence depression or depressive symptoms in BC. Psychosocial factors seem to be the strongest predictors of depressive symptoms [32-34]. In contrast, objective aspects of cancer diagnosis (i.e., disease stage) and cancer treatment (i.e., type of treatment, tamoxifen use) are not associated consistently with the presence of depressive symptoms [32, 34-36].

Quality of sexual life and sexual functioning

Several studies have indicated that BC can negatively impact women's sexual functioning [37]. Although sexuality is considered to be an important aspect of QOL, few studies have examined this topic extensively in BC patients. Most studies on sexuality in BC patients are cross-sectional [38-45]. In general, studies focus on the impact of surgical treatment [41, 44] or chemotherapy [41-43, 45, 46] on sexual functioning (SF; i.e., the experience of sexual difficulties) and sexual activity (i.e., the frequency of sexual activities). As the effects of treatment can lead to premature menopause, loss of fertility, and sexual dysfunction, knowledge about this topic is indispensable. However, knowledge about quality of sexual life is also important, since there may be a discrepancy between sexual problems, on the one hand, and persons' evaluation of their sexual life. In spite of the growing recognition that QOL is of utmost importance, we still have to admit

that knowledge about subjectively perceived quality of sexual life is limited [40, 45, 47, 48].

In general, women with BC experience a wide variety of sexual difficulties, including vaginal dryness, reduced sexual activity, and reduced breast sensitivity [49]. Furthermore, these sexual difficulties appear to be a long-term problem, even after 5 to 10 years following diagnosis [49, 50].

Social Support

Social support is an important resource that may improve QOL in women with early stage BC. Despite a growing interest in this topic, a precise definition is currently lacking. In general, there are two broad perspectives: social support concerns (i) the support that is actually received (i.e., structural support, functional support) or (ii) the individual's subjective appraisal of the social support (perceived social support). Perceived social support can be divided into the perception of availability, when needed, of social support (perceived availability of social support; PASS) and the satisfaction with received social support (SRSS). The latter distinction implies that it is possible that PASS and SRSS have different effects on health and well-being. For instance, it has been suggested that perceived social support may be the most important factor promoting (self-reported) health [51].

Several studies have examined perceived social support in cancer. However, most of them are cross-sectional [52]. Perceived social support has been associated with objective determinants (i.e., network size or frequency of contact with network members) [53], personality [54], the presence of mood disorders [55], and HS [56-61]. With regard to the relationship between perceived social support and survival, findings are rather inconclusive. Whereas some studies [62-64] found a positive relationship between perceived social support and survival, others did not [65].

Aim and design of the study

This thesis describes a prospective longitudinal follow-up study in women with early stage BC. Women with a palpable lump in the breast or an abnormality on a screening mammography were referred by their general practitioner to the Department of Surgery of the outpatient clinics of the St. Elisabeth Hospital

(Tilburg), the Maasland Hospital (Sittard), or the Jeroen Bosch Hospital (Den Bosch) in The Netherlands. These women were eligible for participation in this study. However, women with a medical history of breast disease (either benign or malignant), with signs of dementia, and women who were not able to read and write Dutch were excluded from participation. The data were collected from September 2002 to September 2006. All patients signed an informed consent. Before a mammography and/or a diagnostic needle biopsy were performed, the participating women completed a set of questionnaires. After this baseline measurement additional questionnaires were completed at 1, 3, 6, and 12 months after diagnosis (women with benign breast problems) or surgical treatment (women with early stage BC).

All women completed questionnaires on personality factors (only at baseline), state anxiety, depressive symptoms, fatigue, and QOL. Women with early stage BC were also assessed on disease-specific HS (from 1 month after surgical treatment onwards).

Basic personality factors were assessed with the Neuroticism-Extraversion-Openness-Five Factor Inventory (NEO-FFI) [66, 67], which has been translated into Dutch [68]. This self-report questionnaire consists of 60 statements covering the five broad dimensions of personality that formed the Five-Factor Model (FFM) [66]: Neuroticism (N), Extraversion (E), Openness to new experiences (O), Agreeableness (A), and Conscientiousness (C). Each statement is rated on a 5-point scale ranging from 1 (*strongly disagree*) to 5 (*strongly agree*), resulting in dimension scores of 12 to 60. The psychometrics of the NEO-FFI have been extensively examined. The internal consistency, test-retest reliability, as well as the convergent validity, are acceptable to good [68].

The State Trait Anxiety Inventory (STAI) [69, 70] consists of two 20-item scales for measuring state anxiety and trait anxiety. Initially, the STAI was developed to investigate anxiety phenomena in ‘normal’ adults, but the scale has also proven to be useful in medical and surgical patients [71]. The STAI Trait scale describes how persons generally feel and conceives of anxiety as a personality trait. The STAI State scale is a momentary emotional condition characterized by subjective feelings of apprehension and tension, and heightened autonomic nervous system activity [69].The STAI scales have a 4-point rating

scale ranging from 1 (*almost never*) to 4 (*almost always*). The Dutch version of the STAI has good reliability and validity [70].

The Center for Epidemiological Studies- Depression Scale (CES-D) [72] is a 20-item self-report scale designed to measure the presence and degree of depressive symptoms over the past week. The rating scale ranges from 0 (*seldom or never)* to 3 (*(almost) always*). Scores range from 0 to 60. For the Dutch population, reliability and criterion validity are good [73, 74].

The Fatigue Assessment Scale (FAS) [75] is a 10-item questionnaire assessing a uni-dimensional construct of perceived fatigue and exhaustion. The response scale is a 5-point rating scale ranging from 1 (*never*) to 5 (*always*). Scores on the FAS range from 10 to 50. The psychometric properties are good within a general population, working population, and sarcoidosis patients [76-78].

The World Health Organization Quality of Life assessment instrument-100 (WHOQOL-100) [79, Dutch version 80], is a cross-culturally developed generic multi-dimensional quality of life (QOL) measure. This instrument covers 24 specific facets of QOL, assessed by 96 questions, and one General Health and Overall Quality of Life facet. Each facet is measured with four items using 5-point Likert scales. In general, high facet scores indicate good QOL; except for the facets Pain and Discomfort, Negative Feelings, and Dependence on Medication or Treatments, which are negatively framed. Reliability and validity [80-82] are adequate and sensitivity [83] is high.

The EORTC QLQ-BR23 [84] is a 23-item disease-specific questionnaire measuring HS in BC patients. The BR-23 is a supplementary module of the EORTC QLQ C30, which covers the physical, personal, cognitive, emotional, and social domains [85]. The EORTC QLQ BR-23 incorporates two functional scales (Body Image and Sexual Functioning) and three symptom scales (Arm Symptoms, Breast Symptoms, and Systematic Therapy Side Effects). All scales are transformed to a percentile scale ranging from 1 to 100. High scores in the functioning scales indicate high levels of functioning, whereas high scores in the symptom scales indicate high levels of problems. The remaining items assess the degree of sexual enjoyment and being upset by hair loss. Multi-trait scaling analysis confirmed the hypothesized structure of four of the five scales [84]. Cronbach's alpha coefficients were adequate [84, 86]. In known-group comparisons, there were marked group differences between patients differing in

disease stage [84, 86], previous surgery, performance status, and treatment modality [84]. Additionally, selective scales detected change over time as a function of changes in performance status and treatment-induced change [84].

In addition to this prospective longitudinal follow-up study, we used cross-sectional data. This data set consisted of women who were diagnosed with early stage BC four to five years previously and did not have a recurrence. These women completed the same questionnaires as in the prospective follow-up study. In addition, they completed the RAND 36-Item Health Survey 1.0. The RAND 36 is practically identical to the Medical Outcome Study / Short Form-36. The SF-36 [87] is a 36-item generic questionnaire for assessing HS. The domains refer to physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. A higher score on a particular subscale signifies better health. For each of the eight subscales, scores were summed and transformed to a scale of 0–100, representing the percentage of the highest possible score achieved. Cronbach's alpha coefficients exceeded the 0.70 criterion, except for Social Functioning in a sample of cancer patients [88]. Known-group comparisons yielded consistent support for the validity of the SF-36 [88]. The two general population samples reported the highest levels of health status. The cancer sample yielded the lowest mean SF-36 scale scores [88].

Outline of the thesis

Until now, the number of prospective follow-up studies examining the psychosocial outcomes in women with early stage breast cancer is rather limited. Therefore, the focus in the present thesis is on enriching the paucity of studies in this field. This thesis will be divided into three sections. Part A focuses on QOL. Part B and C focus on two domains of QOL: psychological outcomes and social outcomes, respectively. In Figure 1, a schematic overview of the outline of the present thesis is presented.

The World Health Organization Quality of Life instrument – 100 items (WHOQOL-100) is a cross-cultural generic instrument. However, although recently used in several studies, the WHOQOL-100 was not previously tested for its psychometric properties in Dutch BC patients. Therefore, the psychometric

properties of the WHOQOL-100 were assessed in women with early stage BC, benign breast problems, and BC survivors (**Chapter 2**).

Figure 1. Outline of the thesis

General introduction and outline of the thesis		
Part A QOL	Part B Psychological outcomes	Part C Social outcomes
Chapter 2 Psychometric properties of the WHOQOL-100	Chapter 4 Predictors of depressive symptoms	Chapter 6 The role of personality factors in social support
Chapter 3 Predictors of overall QOL	Chapter 5 The relationship between additional surgical treatment and psychosocial outcomes	Chapter 7 Quality of sexual life and sexual functioning in early stage BC
General discussion and clinical implications		

Chapter 3 discusses which aspects of QOL contribute the most to overall QOL after surgical treatment. Few studies have prospectively assessed QOL in early stage BC. In **Chapter 4** the predictors of depressive symptoms at 12 months after surgical treatment will be examined. **Chapter 5** will describe whether women who have received an additional surgical treatment have more problems in psychosocial functioning compared with women who were more 'effectively' treated. In **chapter 6** the role of personality in the perceived availability of social support and satisfaction with received social support is discussed. The quality of sexual life and sexual functioning is the main theme of **chapter 7**. In the general discussion and summary (**Chapter 8**), the main findings will be summarised and integrated. Implications for clinical research and care will be described. In addition, reflections on limitations and strengths of the present study are provided. The Dutch summary can be found in **chapter 9**.

References

1. Association of Comprehensive Cancer Centres. Incidence of cancer in the Netherlands. Utrecht: Drukkerij De Kempen; 1998.
2. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007;18:581-592.
3. Brody JG, Rudel RA, Michels KB, Moysich KB, Bernstein L, Attfield KR, et al. Environmental pollutants, diet, physical activity, body size, and breast cancer: where do we stand in research to identify opportunities for prevention? Cancer 2007;109:2627-2634.
4. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43-66.
5. McCready D, Holloway C, Shelley W, Down N, Robinson P, Sinclair S, et al. Surgical management of early stage invasive breast cancer: a practice guideline. Can J Surg 2005;48:185-194.
6. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233-1241.
7. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227-1232.
8. Nationaal Borstkanker Overleg Nederland (NABON). Richtlijn behandeling van het mammacarcinoom. Available from www.oncoline.nl. 2008.
9. Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. American Society of Clinical Oncology. J Clin Oncol 1996;14:671-679.
10. Movsas B. Quality of life in oncology trials: a clinical guide. Semin Radiat Oncol 2003;13:235-247.
11. Van der Steeg AF, De Vries J, Roukema JA. Quality of life and health status in breast carcinoma. Eur J Surg Oncol 2004;30:1051-1057.

12. Van der Steeg AF, De Vries J, Roukema JA. The value of quality of life and health status measurements in the evaluation of the well-being of breast cancer survivors. Eur J Surg Oncol 2008;34:1225-1230.
13. WHOQOL group. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med 1995;41:1403-1409.
14. De Vries J. Assessment in behavioural medicine. In: Vingerhoets AJJM, editor. Quality of life assessment. Hove, UK: Brunner-Routledge, 2001. p. 353-370.
15. Al-Ghazal SK, Fallowfield L, Blamey RW. Comparison of psychological aspects and patient satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. Eur J Cancer 2000;36:1938-1943.
16. Fobair P, Stewart SL, Chang S, D'Onofrio C, Banks PJ, Bloom JR. Body image and sexual problems in young women with breast cancer. Psycho-oncology 2006;15:579-594.
17. Fallowfield LJ. Psychosocial adjustment after treatment for early breast cancer. Oncology (Williston Park) 1990;4:89-97; discussion 97-8, 100.
18. Ganz PA, Kwan L, Stanton AL, Krupnick JL, Rowland JH, Meyerowitz BE, et al. Quality of life at the end of primary treatment of breast cancer: first results from the moving beyond cancer randomized trial. J Natl Cancer Inst 2004;96:376-387.
19. Ganz PA, Schag AC, Lee JJ, Polinsky ML, Tan SJ. Breast conservation versus mastectomy. Is there a difference in psychological adjustment or quality of life in the year after surgery? Cancer 1992;69:1729-1738.
20. Lu W, Cui Y, Chen X, Zheng Y, Gu K, Cai H, et al. Changes in quality of life among breast cancer patients three years post-diagnosis. Breast Cancer Res Treat 2009;114:357-369.
21. Baker F, Marcellus D, Zabora J, Polland A, Jodrey D. Psychological distress among adult patients being evaluated for bone marrow transplantation. Psychosomatics 1997;38:10-19.
22. Petrie KJ, Buick DL, Weinman J, Booth RJ. Positive effects of illness reported by myocardial infarction and breast cancer patients. J Psychosom Res 1999;47:537-543.

23. King MT, Kenny P, Shiell A, Hall J, Boyages J. Quality of life three months and one year after first treatment for early stage breast cancer: influence of treatment and patient characteristics. Qual Life Res 2000;9:789-800.
24. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. BMJ 2005;330:702.
25. Massie MJ. Prevalence of depression in patients with cancer. J Natl Cancer Inst Monogr 2004:57-71.
26. Coyne JC, Palmer SC, Shapiro PJ, Thompson R, DeMichele A. Distress, psychiatric morbidity, and prescriptions for psychotropic medication in a breast cancer waiting room sample. Gen Hosp Psychiatry 2004;26:121-128.
27. Schag CA, Ganz PA, Polinsky ML, Fred C, Hirji K, Petersen L. Characteristics of women at risk for psychosocial distress in the year after breast cancer. J Clin Oncol 1993;11:783-93.
28. Deshields T, Tibbs T, Fan MY, Taylor M. Differences in patterns of depression after treatment for breast cancer. Psycho-oncology 2006;15:398-406.
29. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000;160:2101-2107.
30. Ayres A, Hoon PW, Franzoni JB, Matheny KB, Cotanch PH, Takayanagi S. Influence of mood and adjustment to cancer on compliance with chemotherapy among breast cancer patients. J Psychosom Res 1994;38:393-402.
31. Hjerl K, Andersen EW, Keiding N, Mouridsen HT, Mortensen PB, Jorgensen T. Depression as a prognostic factor for breast cancer mortality. Psychosomatics 2003;44:24-30.
32. Golden-Kreutz DM, Andersen BL. Depressive symptoms after breast cancer surgery: relationships with global, cancer-related, and life event stress. Psycho-oncology 2004;13:211-220.

33. Finch JF, Graziano WG. Predicting depression from temperament, personality, and patterns of social relations. J Pers 2001;69:27-55.
34. Bardwell WA, Natarajan L, Dimsdale JE, Rock CL, Mortimer JE, Hollenbach K, et al. Objective cancer-related variables are not associated with depressive symptoms in women treated for early-stage breast cancer. J Clin Oncol 2006;24:2420-2427.
35. Christensen S, Zachariae R, Jensen AB, Vaeth M, Møller S, Ravnsbaek J, et al. Prevalence and risk of depressive symptoms 3-4 months post-surgery in a nationwide cohort study of Danish women treated for early stage breast-cancer. Breast Cancer Res Treat 2009;113:339-355.
36. Wong-Kim EC, Bloom JR. Depression experienced by young women newly diagnosed with breast cancer. Psycho-oncology 2005;14:564-573.
37. Thors CL, Broeckel JA, Jacobsen PB. Sexual functioning in breast cancer survivors. Cancer Control 2001;8:442-448.
38. Barni S, Mondin R. Sexual dysfunction in treated breast cancer patients. Ann Oncol 1997;8:149-153.
39. Takahashi M, Ohno S, Inoue H, Kataoka A, Yamaguchi H, Uchida Y, et al. Impact of breast cancer diagnosis and treatment on women's sexuality: a survey of Japanese patients. Psycho-oncology 2008;17:901-907.
40. Ganz PA, Desmond KA, Belin TR, Meyerowitz BE, Rowland JH. Predictors of sexual health in women after a breast cancer diagnosis. J Clin Oncol 1999;17:2371-2380.
41. Ganz PA, Rowland JH, Desmond K, Meyerowitz BE, Wyatt GE. Life after breast cancer: understanding women's health-related quality of life and sexual functioning. J Clin Oncol 1998;16:501-514.
42. Broeckel JA, Thors CL, Jacobsen PB, Small M, Cox CE. Sexual functioning in long-term breast cancer survivors treated with adjuvant chemotherapy. Breast Cancer Res Treat 2002;75:241-248.
43. Malinovszky KM, Gould A, Foster E, Cameron D, Humphreys A, Crown J, et al. Quality of life and sexual function after high-dose or conventional chemotherapy for high-risk breast cancer. Br J Cancer 2006;95:1626-1631.
44. Yurek D, Farrar W, Andersen BL. Breast cancer surgery: comparing surgical groups and determining individual differences in postoperative

sexuality and body change stress. J Consult Clin Psychol 2000;68:697-709.

45. Young-McCaughan S. Sexual functioning in women with breast cancer after treatment with adjuvant therapy. Cancer Nurs 1996;19:308-319.
46. Joly F, Espie M, Marty M, Heron JF, Henry-Amar M. Long-term quality of life in premenopausal women with node-negative localized breast cancer treated with or without adjuvant chemotherapy. Br J Cancer 2000;83:577-582.
47. Andersen BL, Carpenter KM, Yang HC, Shapiro CL. Sexual well-being among partnered women with breast cancer recurrence. J Clin Oncol 2007;25:3151-157.
48. Burwell SR, Case LD, Kaelin C, Avis NE. Sexual problems in younger women after breast cancer surgery. J Clin Oncol 2006;24:2815-21.
49. Ganz PA, Greendale GA, Petersen L, Kahn B, Bower JE. Breast cancer in younger women: reproductive and late health effects of treatment. J Clin Oncol 2003;21:4184-4193.
50. Bloom JR, Stewart SL, Chang S, Banks PJ. Then and now: quality of life of young breast cancer survivors. Psycho-oncology 2004;13:147-160.
51. Bovier PA, Chamot E, Perneger TV. Perceived stress, internal resources, and social support as determinants of mental health among young adults. Qual Life Res 2004;13:161-170.
52. Courtens AM, Stevens FC, Crebolder HF, Philipsen H. Longitudinal study on quality of life and social support in cancer patients. Cancer Nurs 1996;19:162-169.
53. Cutrona C. Objective determinants of perceived social support. J Person Soc Psychol 1986;50:349-355.
54. Roberts S, Wilson R, Fedurek P, Dunbar R. Individual differences and personal social network size and structure. Person Individ Dif 2008;44:954-964.
55. Hann D, Baker F, Denniston M, Gesme D, Reding D, Flynn T, et al. The influence of social support on depressive symptoms in cancer patients: age and gender differences. J Psychosom Res 2002;52:279-283.

56. Manning-Walsh J. Social support as a mediator between symptom distress and quality of life in women with breast cancer. J Obstet Gynecol Neonatal Nurs 2005;34:482-493.
57. Lewis JA, Manne SL, DuHamel KN, Vickburg SM, Bovbjerg DH, Currie V, et al. Social support, intrusive thoughts, and quality of life in breast cancer survivors. J Behav Med 2001;24:231-245.
58. Ogce F, Ozkan S, Baltalarli B. Psychosocial stressors, social support and socio-demographic variables as determinants of quality of life of Turkish breast cancer patients. Asian Pac J Cancer Prev 2007;8:77-82.
59. Karnell LH, Christensen AJ, Rosenthal EL, Magnuson JS, Funk GF. Influence of social support on health-related quality of life outcomes in head and neck cancer. Head Neck 2007;29:143-146.
60. Sammarco A. Perceived social support, uncertainty, and quality of life of younger breast cancer survivors. Cancer Nurs 2001;24:212-219.
61. Michael YL, Berkman LF, Colditz GA, Holmes MD, Kawachi I. Social networks and health-related quality of life in breast cancer survivors: a prospective study. J Psychosom Res 2002;52:285-293.
62. Weihs KL, Enright TM, Simmens SJ. Close relationships and emotional processing predict decreased mortality in women with breast cancer: preliminary evidence. Psychosom Med 2008;70:117-124.
63. Weihs KL, Simmens SJ, Mizrahi J, Enright TM, Hunt ME, Siegel RS. Dependable social relationships predict overall survival in Stages II and III breast carcinoma patients. J Psychosom Res 2005;59:299-306.
64. Kroenke CH, Kubzansky LD, Schernhammer ES, Holmes MD, Kawachi I. Social networks, social support, and survival after breast cancer diagnosis. J Clin Oncol 2006;24:1105-1111.
65. Cassileth BR, Lusk EJ, Miller DS, Brown LL, Miller C. Psychosocial correlates of survival in advanced malignant disease? N Engl J Med 1985;312:1551-1555.
66. Costa PT, McCrae RR. The NEO Personality Inventory Manual. Odessa, FL: Psychological Assessment Resources Inc.; 1985.
67. Costa PT, McCrae RR. Revised NEO Personality Inventory (NEO-PI-R) and NEO Five Factor Inventory (NEO-FFI) professional manual. Odessa, FL: Psychological Assessment Resources Inc.; 1992.

68. Hoekstra HA, Ormel J. De Fruyt F. Handleiding NEO persoonlijkheidsvragenlijsten NEO-PI-R en NEO-FFI [manual NEO Personality questionnaires NEO-PI-R and NEO-FFI]. Lisse, The Netherlands. Swets Test Services; 1996.
69. Spielberger CD, Gorsuch RL, Lushene RE. STAI manual for the State-Trait Anxiety Inventory. Palo-Alto, CA: Consulting Psychologists Press; 1970.
70. Van der Ploeg HM, Defares PB, Spielberger CD. ZBV, a Dutch- language adaptation of the Spielberger State-Trait Anxiety Inventory. Lisse, The Netherlands: Swets & Zeitlinger; 1980.
71. Stark D, Kiely M, Smith A, Velikova G, House A, Selby P. Anxiety disorders in cancer patients: their nature, associations, and relation to quality of life. J Clin Oncol 2002;20:3137-3148.
72. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385-401.
73. De Rijk AE, Schreurs KMG, Bensing JM. What is behind "i'm so tired"? fatigue experiences and their relations to the quality and quantity of external stimulation. J Psychosom Res 1999;47:509-523.
74. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. Psychol Med 1997;27:231-235.
75. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: the Fatigue Assessment Scale. J Psychosom Res 2003;54:345-352.
76. De Vries J, Michielsen H, Van Heck GL, Drent M. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). Br J Health Psychol 2004;9(Pt 3):279-291.
77. Michielsen HJ, De Vries J, Drent M, Peros-Golubicic T. Psychometric qualities of the Fatigue Assessment Scale in Croatian sarcoidosis patients. Sarcoidosis Vasc Diffuse Lung Dis 2005;22:133-138.
78. Michielsen H, De Vries J, van Heck GL, Van de Vijver A, Sijtsma K. Examination of the dimensionality of fatigue: the construction of the Fatigue Assessment Scale (FAS). Eur J Psychol Assess 2004;20:39-48.

79. WHOQOL Group. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc Sci Med 1998;46:1569-1585.
80. De Vries J, Van Heck GL. The World Health Organization Quality of Life assessment instrument (WHOQOL-100): validation study with the Dutch version. Eur J Psychol Assess 1997;13:164-178.
81. Power M, Harper A, Bullinger M. The World Health Organization WHOQOL-100: tests of the universality of Quality of Life in 15 different cultural groups worldwide. Health Psychol 1999;18:495-505.
82. Den Oudsten BL, Van Heck GL, Van der Steeg AF, Roukema JA, De Vries J. The WHOQOL-100 has good psychometric properties in breast cancer patients. J Clin Epidemiol 2009;62:195-205.
83. O'Carroll RE, Smith K, Couston M, Cossar JA, Hayes PC. A comparison of the WHOQOL-100 and the WHOQOL-BREF in detecting change in quality of life following liver transplantation. Qual Life Res 2000;9:121-124.
84. Sprangers MA, Groenvold M, Arraras JI, Franklin J, Te Velde A, Muller M, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996;14:2756-2768.
85. Sprangers MA, Cull A, Bjordal K, Groenvold M, Aaronson NK. The European Organization for Research and Treatment of Cancer. Approach to quality of life assessment: guidelines for developing questionnaire modules. EORTC Study Group on Quality of Life. Qual Life Res 1993;2:287-295.
86. Yun YH, Bae SH, Kang IO, Shin KH, Lee R, Kwon SI, et al. Cross-cultural application of the Korean version of the European Organization for Research and Treatment of Cancer (EORTC) Breast-Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23). Support Care Cancer 2004;12:441-445.
87. Ware JE. SF-36 Health Survey: Manual & interpretation guide. Boston, MA: The Health Institute, New England Medical Center; 1993.

88. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055-1068.

Chapter 2
The WHOQOL-100 has good psychometric properties in breast cancer patients*

* Den Oudsten BL, Van Heck GL, Van der Steeg AFW, Roukema JA, De Vries J. The WHOQOL-100 has good psychometric properties in breast cancer patients. *J Clin Epidemiol* 2009; 62:195-205.

Abstract

Objective: This prospective follow-up study examines the psychometric properties of the WHOQOL-100 for assessing quality of life (QOL) in women suspected of having breast cancer and disease-free breast cancer survivors. *Method:* The WHOQOL-100 was tested at five points in time in women with a palpable lump in the breast or an abnormality on a screening mammography (N = 356) and breast cancer survivors (N = 140). Furthermore, all participants completed measures of anxiety (STAI) and depression (CES-D). Moreover, women who were diagnosed with breast cancer also completed the EORTC-QLQ-BR-23 at time points 2 to 5. Reliability (internal consistency; test-retest reliability) and construct validity were tested. *Results*: Confirmatory factor analyses on the WHOQOL-100 items showed a good fit with models reflecting six factors (physical health, psychological health, level of independence, social relationships, environment, spirituality/religion/personal beliefs) or four factors (physical health, psychological health, social relationships, environment). Internal consistency was adequate. Test-retest correlations were high. The WHOQOL-100 correlated highly with related constructs and showed low correlations with unrelated constructs. *Conclusion*: The WHOQOL-100 is a reliable and valid instrument for measuring QOL in women suspected of having breast cancer and disease-free breast cancer survivors.

Introduction

Breast cancer is the most common malignancy in women [1] and the most frequent cause of death in women aged 35 to 60 years in Europe [2]. In the Netherlands, one in every nine women will develop breast cancer before the age of 85 [3]. The prevalence of breast cancer increases with age from 3-4% at age 50-69 to 6% of women older than 70 [4]. Following a breast cancer diagnosis, up to four in ten women is experiencing symptoms of anxiety and depression [5]. For this reason, and also due to the growing number of breast cancer survivors [6], it has become increasingly important to include in research not only medical endpoints (e.g., morbidity and mortality), but also patient-based outcome measures, such as quality of life (QOL). Therefore, the aim of this prospective follow-up study was to examine the psychometric properties of the *World Health Organization Quality of Life assessment instrument* (WHOQOL-100), a multidimensional QOL instrument.

QOL has become a popular concept in research. However, the debate on how to conceptualize QOL is still ongoing. Many different conceptualizations are covered by numerous instruments, for instance, the Short Form Health Survey – 36 items (SF-36) [7], and the EORTC Quality of Life Questionnaire- 30 items [8], and its complementary breast-cancer module (QLQ BR23) [9]. Although a gold standard does not exist, the majority of the literature supports the multi-dimensional aspect of QOL, in which QOL consists of at least a physical, an emotional, and a social domain [10]. Another commonly accepted characteristic is that QOL should reflect the patient's own evaluation of life. However, strong disagreement exists, regarding the exact content of the QOL concept and its operationalization in an assessment instrument.

In general, QOL instruments can be divided into 'objective' and 'subjective' QOL measures. Some authors [11-13] state that these objective measures, for instance, the SF-36, the EORTC Quality of Life Questionnaire 30 items (QLQ-30), or the breast-cancer specific module (BR-23) are not reflecting QOL. In their view, these objective QOL measures focus, strictly speaking, on health status (HS). Therefore, several authors have suggested that objective measures, reflecting predominantly symptoms and functioning, should not be used as a measure of QOL [12, 13].

In 1991, The World Health Organization (WHO) acknowledged the importance of patient's self-evaluation of life by initiating a project, which aimed to develop a generic cross-cultural QOL instrument that would be broadly applicable across disease types and varying severities of illness. This multi-dimensional instrument, the *World Health Organization Quality of Life assessment instrument* (WHOQOL-100) [14], reflects the view that QOL is a broad-ranging concept that incorporates *subjectively* experienced QOL. This is also reflected in the definition of QOL formulated by the WHOQOL-Group [15], in which QOL is conceptualized as 'an individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards and concerns. It is a broad-ranging concept incorporating in a complex way the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of the environment' (p. 1405). In addition, the WHOQOL-100 includes both positive (e.g., having the opportunity to go on holiday or to perform leisure activities) and negative dimensions (e.g., pain and bodily discomfort) [15]. This positive approach is also reflected in the way the items are formulated (e.g., 'How satisfied are you with your energy level?'). Each QOL facet contains both positive and negative items. In sum, the WHOQOL-100 is not only focusing on the manifestations of distress caused by disease. This is of utmost importance because it is a well-established phenomenon that cancer can also have positive effects on a person's life [16, 17].

The WHOQOL-100 is cross-culturally developed and has excellent psychometric properties in various populations, such as patients with a liver transplantation [18, 19], chronic pain patients [20], and psychiatric patients [21]. Tazaki and colleagues [22] reported that the WHOQOL-100 was sensitive enough to evaluate QOL in cancer patients. Cronbach's alpha coefficient for the total scale was .97. High correlations were found between the psychological domain and the environmental domain (r = 0.70), the physical domain and the level of independence (r = 0.60) and social relations and the environment (r = 0.69). Some of the results suggested that mean QOL scores in cancer patients differ depending on the site and treatment. However, test-retest reliability and construct validity was not assessed.

Therefore, in the present study, the WHOQOL-100 is extensively tested for its properties. We expected that a 6-factor model, consisting of Physical Health, Psychological Health, Level of Independence, Social Relationships, Environment, and Spirituality/Religion/Personal Beliefs would be confirmed in structural equation modeling. Furthermore, we expected that a more recently suggested 4-factor model, consisting of Physical Health, Psychological Health, Social Relationships, and Environment [23] would show an even better fit. In addition, it was expected that particular facets of the WHOQOL-100, such as Body Image and Appearance, would be highly correlated with corresponding facets, like the EORTC QLQ BR-23 dimensions Body Image and Upset by Hair Loss. Likewise, relatively high associations were predicted between scores on the STAI and CES-D, on the one hand, and the WHOQOL-100 facet Negative Feelings, on the other hand. In contrast, it was expected that relatively low correlations would exist between WHOQOL-100 facets, like, for instance, the WHOQOL-100 facet Home Environment (QOL) and rather unrelated facets like the SF-36 domain Bodily Pain and the EORTC QLC-BR 23 domain Breast Problems.

Method

Participants

Two samples were used in this study. The first sample consisted of women with a palpable lump in the breast or an abnormality on a screening mammography who were referred by their general practitioner to the surgical outpatient clinics of St. Elisabeth Hospital (Tilburg, The Netherlands), the Maasland Hospital (Sittard, The Netherlands), or the Jeroen Bosch Hospital (Den Bosch, The Netherlands). The present study in which the WHOQOL-100 is validated, is part of a larger study focusing on the role of personality in patients' QOL. The data were collected from September 2002 until September 2006. Of the 546 eligible women, 356 (65.2%) completed the first set of questionnaires. The questionnaires were completed before the women visited the surgeon or radiologist, i.e. before the diagnosis, benign or malignant, was known. This is comparable to other studies with T1 before diagnosis (e.g., 24]. The main reasons for not participating were the length of questionnaires and the amount of stress women experienced at their first visit at the hospital. Of these 356 women, 200 subsequently appeared to have

benign breast problems (BBP) and 156 were diagnosed with breast cancer (BC). Woman who had a history of abnormalities in the breast, benign or malignant, or had a breast tumor that was too large (>5 centimeter) for breast conserving therapy, were excluded from the study. In order to participate, the women had to be able to write and read in Dutch. After the baseline measurement before diagnosis (T1), women completed questionnaires 1 (T2), 3 (T3), 6 (T4), and 12 (T5) months after diagnosis (BBP) or after surgical treatment (BC). When women were asked to participate in the study and completed the first set of questionnaires, it was unknown whether a woman had BC or BBP. Once diagnosis was known, diagnosis was the reference point for subsequent measurement times for benign patients. For BC patients, the reference point was surgical treatment because otherwise follow-up measures would interfere with timing of treatment modalities. Participation in the study was not known by the surgeon in attendance and, therefore, could not have affected treatment and clinical follow-up. All participants gave written informed consent.

The second group consisted of all disease-free early stage breast cancer survivors (BCS) who were diagnosed between January 2000 and December 2001 ($N = 272$) at the Department of Surgery of the St. Elisabeth Hospital, Tilburg (The Netherlands). In December 2005, all patients were assessed with respect to their well-being. Women who did not have an operation, who were diagnosed with locally advanced breast cancer tumors larger than 5 centimeter, or developed recurrent breast cancer or systemic disease in the period of four to five years since treatment, were not included. One hundred and ninety-four women were eligible. However, three patients were diagnosed with dementia, nine women were deceased, and four were lost to follow-up. The remaining 178 women were all contacted by phone and asked whether they wanted to participate. Reasons for refusal were ‘not interested’ ($n = 10$), ‘too hard / do not want to be confronted with the past’ ($n = 15$), and ‘other reasons’ ($n = 7$). Of the 146 women who agreed to participate, 140 signed the informed consent form and returned completed questionnaires (78.7%).

Measures

All groups completed the following questionnaires: World Health Organization Quality of Life assessment instrument-100 (WHOQOL-100) [14, 15], State Trait

Anxiety Inventory (STAI) [25], and the Center for Epidemiologic Studies Depression scale (CES-D) [26]. The European Organization for Research and Treatment Quality of Life Breast Cancer instrument (EORTC-QLQ-BR23) [9] was not included in the first set of questionnaires, because this is a disease-specific questionnaire and diagnosis was unknown at T1. Therefore, the EORTC-QLQ-BR23 was not completed by the BBP group. In addition, the BCS group also completed the SF-36 [7].

Quality of life

Quality of life was measured using the WHOQOL-100 [14, 27]. This instrument covers 24 facets, assessed by 96 questions, and one General health and Overall Quality of Life facet. Each facet is measured with four items with a 5-point Likert scale. Twenty-four facets were initially scored in six domains of QOL: Physical Health, Psychological Health, Levels of Independence, Social Relationships, Environment, and Spirituality, Religion and Personal Beliefs [14]. Nowadays, it is well accepted to convert these 24 facets into four domains as described by the WHOQOL group [23, 28]. High facet scores indicate good QOL; except for the facets Pain and Discomfort, Negative Feelings, and Dependence on Medication or Treatments, which are negatively framed. The time frame of reference is the previous two weeks. Reliability and validity [23, 27] are adequate, and sensitivity [18] of the instrument is high.

Health status

The EORTC QLQ-BR23 [9] is a 23-item disease-specific questionnaire measuring health status in breast cancer patients. The BR-23 is a supplementary module of the EORTC QLQ C30, which covers the physical, personal, cognitive, emotional, and social domains [29]. The EORTC QLQ BR-23 incorporates two functional scales (Body Image and Sexual Functioning) and three symptom scales (Arm Symptoms, Breast Symptoms, and Systematic Therapy Side Effects). The remaining items assess sexual enjoyment and being upset by hair loss. Multitrait scaling analysis confirmed the hypothesized structure of four of the five scales [9]. Cronbach's alpha coefficients were adequate [9, 30]. In known-group comparisons, there were marked group differences between patients differing in disease stage [9, 30], previous surgery, performance status, and treatment

modality [9]. Additionally, selective scales detected change over time as a function of changes in performance status and treatment-induced change [9].

The SF-36 [7] is a 36-item generic questionnaire for assessing health status. The domains refer to physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. A higher score on a particular subscale signifies better health. For each of the eight subscales, scores were summed and transformed to a scale of 0–100, representing the percentage of the highest possible score achieved. Cronbach's alpha coefficients exceeded the 0.70 criterion, except for Social Functioning in a sample of cancer patients [31]. Known-group comparisons yielded consistent support for the validity of the SF-36 [31]. The two general population samples reported the highest levels of health status. The cancer sample yielded the lowest mean scale SF-36 scores [31].

Mood

The STAI [25, Dutch version by 32] consists of two 20-item scales for measuring state anxiety and trait anxiety. The STAI State scale was used in this study. This scale assesses how persons feel at a particular moment in time. The STAI has a 4-point rating scale ranging from 1 (*not at all/almost never*) to 4 (*very much so/almost always*). The Dutch version of the STAI has good reliability and validity [32).

The CES-D [26] is a 20-item self-report scale designed to measure the presence and degree of depressive symptoms over the past week. The rating scale ranges from 1 (*seldom or never)* to 4 (*(almost) always*). Scores can range from 0 to 60; scores $\geq$ 16 are suggestive of depressive symptoms. For the Dutch population, reliability and criterion validity are good [33, 34]. Beekman et al. [34] found excellent sensitivity for major depression in a sample of elderly persons. In addition, the internal consistency in a large Dutch patient population was good, Cronbach's alpha was .91 [33]. In breast cancer survivors with a recurrence and disease-free survivors, the internal consistency was .90 and .91, respectively [35].

Socio-demographic variables

Patients were asked to report age, marital status, education, and paid work (*yes/no*).

Statistical analysis

Calculation of frequencies was used to present the demographic data before diagnosis. Student *t*-tests and Chi-square tests were used to compare (i) the participants and non-participants and (ii) the BBP group and the BC group. In general, statistical analyses were performed in all groups (BBP, BC, and BCS). However, for the confirmatory factor analysis (CFA) and test-retest reliability, we performed the analyses in respectively the BCS group and the BBP group, because for these analyses we hypothesized that it was important to have relatively stable groups. For this reason, test-retest reliability was calculated for T2 and T3. Correlations of at least 0.80 were seen as indicative for good test-retest reliability. A CFA was conducted in BCS to test whether the original six-domain structure and the recently revised four-domain structure are suited to a population with (former) breast problems. The hypothesized models are presented in Figures 1 and 2. Goodness of fit was verified by the following fit indices: the Comparative Fit Index (CFI) and the Root Mean Square Error of Approximation (RMSEA). The models have a satisfactory to good fit when: CFI > .90 and RMSEA < .06 [34]. Concerning construct validity, Pearson correlations were calculated between the WHOQOL-100, on the one hand, and the EORTC QLQ BR-23, STAI-state, and CES-D, on the other hand. Moderate correlations (r = .30 to .49) are indicative for convergent validity, while small correlations (r = .10 to .29) are indicative for divergent validity [37, 38]. With regard to the reliability of the WHOQOL-100, two types of reliability were examined: internal consistency (all groups) and test-retest reliability (BBP group). Cronbach's alpha coefficients were computed to estimate the internal-consistency reliability of the QOL domains and facets [39]. Depending on the number of questions in a (sub)scale, Cronbach's alpha should be at least .70. The data were processed by means of the Statistical Package for the Social Sciences (SPSS, version 14.0 for Windows), except for the CFA (AMOS 7.0) [40].

Results

Participants

Patient characteristics of the three groups (BC, BBP, and BCS group) are shown in Table 1. Of the 356 included patients, 156 had breast cancer, and 200 women appeared to have benign breast problems. Women who participated in the study

were significantly younger [t (1, 546) = 2.96, $p < 0.01$] and more often appeared to have breast cancer ($\chi^2 = 6.01$, $p = 0.014$) than the non-participants. After diagnosis, the participating women were divided in two groups: women with BBP and women with BC. Women with BBP were younger [t (1, 354) = 6.25, $p < 0.001$) and more often employed ($\chi^2 = 9.25$, $p = 0.002$) compared with the BC group. In both subgroups, the majority of the women lived with a partner and had one or more children. Women who participated in the BCS were significantly younger [t (1, 270 = 2.13), $p < 0.05$)] than non-participants.

Table 1. Patient characteristics (T1)

Characteristics	BC + BBP group (N=356)	BC group (N=156)	BBP group (N=200)	BCS (N=140)
Age (mean, SD, range)	54.9 ± .56 (19-87)	58.7 ± 9.5 (34-87)	52.0 ± 10.5 (19-77)	56.6 ±11.4 (26-85)
Living with a partner (yes/no/missing)	277/60/19	116/31/9	161/29/10	101/37/1
Children (yes/no/missing)	297/51/8	131/21/4	166/30/4	116/23/1
Educational level* (low/middle/high/ Missing))	114/156/59/27	57/64/25/10	57/92/34/17	56/59/24/0
Paid work (yes/no/missing)	165/182/0	56/96/4	109/86/5	45/93/1

*Note: *Low = up to 10 years of education; middle = 10 to 14 years of education; high = more than 14 years of education*

Confirmatory factor analysis

In order to test the six-domain and four-domain structure of the WHOQOL-100 (See Fig. 1 and Fig. 2, respectively), structural equation modelling (SEM) analyses were conducted. Careful inspection of modification indices as provided by AMOS 7 suggested a number of modifications to improve the initial model six-domain model without correlated errors which did not meet our criteria for an acceptable fit (CFI = 0.81; RMSEA = .0089). Adding error covariances between Facet 4 (Positive Feelings) and the Social Relationships Domain, Facet 4 (Positive Feelings) and the Environment Domain, and between the Facets 4

(Positive Feelings) and 5 (Cognitive Functions), 4 (Positive Feelings) and 11 (Dependence/Medication), 14 (Social Support) and 19 (Health and Social Care), 6 (Self-Esteem) and 24 (Spirituality/Religion/Personal Beliefs), 10 (Activities of Daily Living) and 16 Physical Safety/Security), 7 (Body Image/Appearance) and 19 (Health and Social Care) improved model fit significantly: CFI = 0.90 and RMSEA = 0.068. For the associations between the latent variable Quality of Life and the six domains the following standardized regression weights were obtained: 1.0 (Physical Health), .93 (Level of Independence), .83 (Psychological Health), .68 (Environment), .52 (Social Relationships), and .43 (Spiritual Domain). Table 2 contains the standardized regression weights for the 24 facets of the WHOQOL-100. Inspection of these parameter estimates reveals that in case of Physical Health, Facet 1 (Pain and Discomfort) and Facet 2 (Energy and Fatigue) had higher loadings on their corresponding latent factor than Facet 3 (Sleep and Rest). With respect to Psychological Health, Level of Independence, Social Relationships, and Environment the highest loadings were found, respectively, for Facet 8 (Negative Feelings), Facet 10 (Activities of Daily Living), and Facet 13 (Personal Relationships), and Facet 19 (Health and Social Care).

Also in case of the testing of the four-factor structure, similar fit indices were found in case of the present population, compared with the corresponding analysis on the original field trial data set of the WHOQOL-100 [28]. When seven pairs of error variances were allowed to covary a fair to good fit was obtained: CFI = 0.90 and RMSEA = 0.065. Correlated error variances had to be added between the Facets 4 (Positive Feelings) and 5 (Cognitive Functions), 4 (Positive Feelings) and 11 (Dependence/Medication), 7 (Body Image/Appearance) and 11 (Dependence/Medication), 6 (Self-Esteem) and 24 (Spirituality/Religion/Personal Beliefs), 16 (Physical Safety/Security) and 17 (Home Environment), 17 (Home Environment) and 22 (Physical Environment), and 16 (Physical Safety/Security) and 22 (Physical Environment). For the associations between the latent variable Quality of Life and the four domains the following standardized regression weights were obtained: .97 (Psychological Health), .87 (Environment), .76 (Social Relationships), and .71 (Physical Health). Table 3 presents the standardized regression weights for the 24 facets of the WHOQOL-100.

Table 2. Standardized regression weights of the facets on their latent variables (Domains): Six-domain model

Domain	Facet	I	II	III	IV	V	VI
I Physical Health	1 Pain and Discomfort	-.72					
	2 Energy and Fatigue	.87					
	3 Sleep and Rest	.35					
II Psychological Health	4 Positive Feelings		.67				
	5 Cognitive Functions		.46				
	6 Self-Esteem		.68				
	7 Body Image/Appearance		.51				
	8 Negative Feelings		-.70				
III Level of Independence	9 Mobility			.48			
	10 Activities of Daily Living			.97			
	11 Dependence/Medication			-.56			
	12 Working Capacity			.79			
IV Social Relationships	13 Personal Relationships				.88		
	14 Social Support				.70		
	15 Sexual Activity				.60		
V Environment	16 Physical Safety/Security					.52	
	17 Home Environment					.61	
	18 Financial Resources.					.59	
	19 Health and Social Care					.53	
	20 New Information/Skills					.84	
	21 Participation Recreation					.69	
	22 Physical Environment					.45	
	23 Transport					.55	
VI Spiritual Domain	24 Spirituality/ Religion/ Personal Beliefs						.35

Table 3. Standardized regression weights of the facets on their latent variables (Domains): Four-domain model

Domain	Facet	I	II	III	IV
I Physical Health	1 Pain and Discomfort	-.71			
	2 Energy and Fatigue	.86			
	3 Sleep and Rest	.33			
	9 Mobility	.49			
	10 Activities of Daily Living	.95			
	11 Dependence/Medication	-.59			
	12 Working Capacity	.79			
II Psychological	4 Positive Feelings		.83		
Health	5 Cognitive Functions		.47		
	6 Self-Esteem		.67		
	7 Body Image/Appearance		.43		
	8 Negative Feelings		-.60		
	24 Spirituality/Religion/Personal Beliefs		.22		
III Social	13 Personal Relationships			.90	
Relationships	14 Social Support			.70	
	15 Sexual Activity			.59	
IV Environment	16 Physical Safety/Security				.51
	17 Home Environment				.60
	18 Financial Resources.				.56
	19 Health and Social Care				.53
	20 New Information/Skills				.83
	21 Participation Recreation				.74
	22 Physical Environment				.42
	23 Transport				.53

Figure 1. A second order six-domain model for the WHOQOL-100

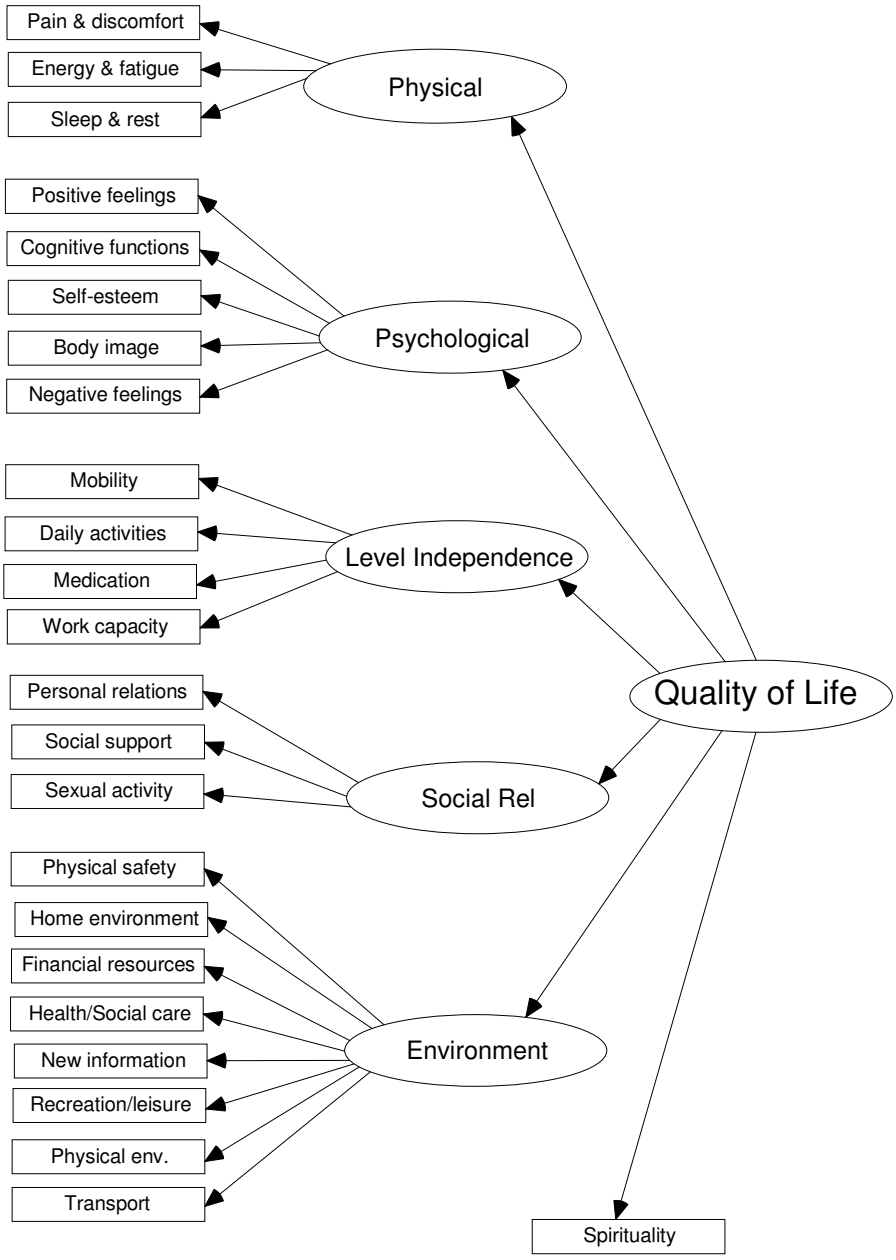
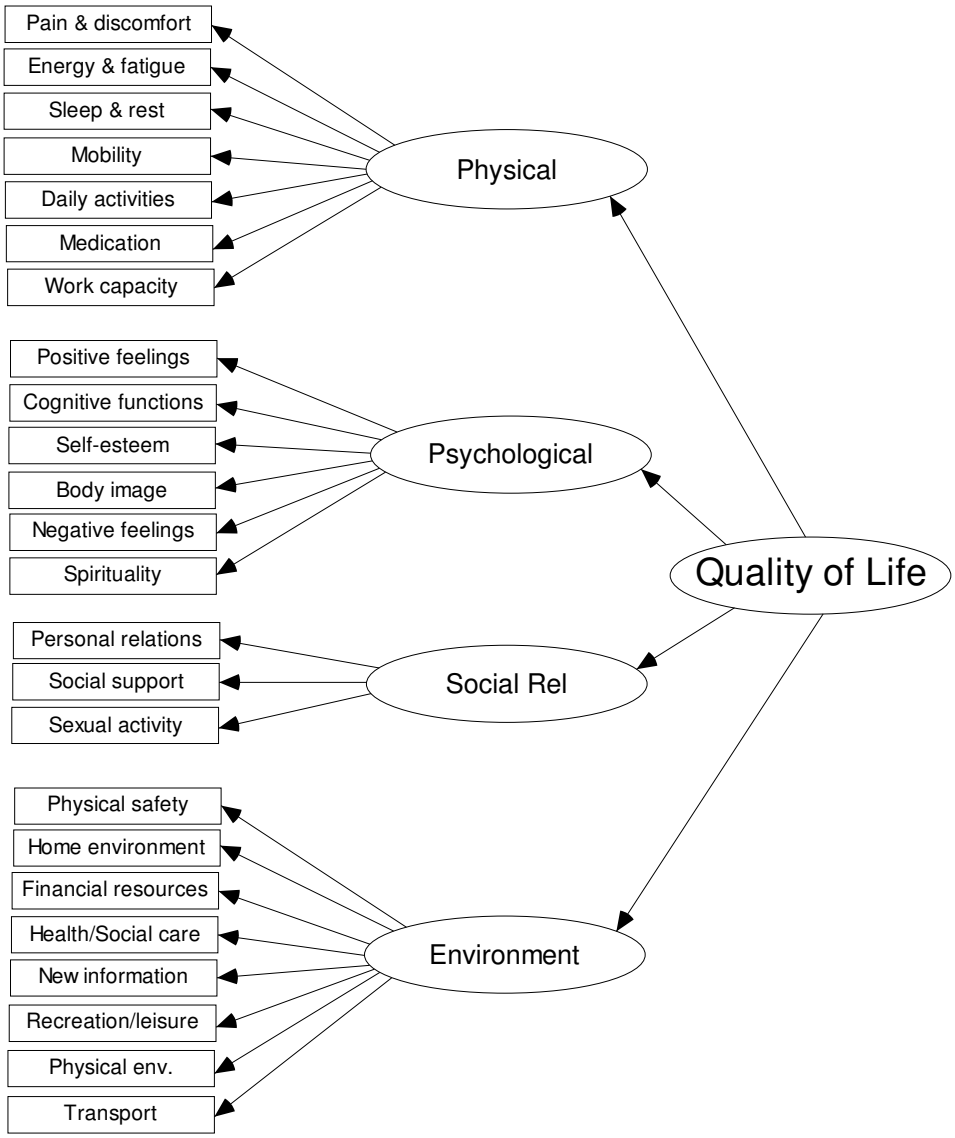


Figure 2. A second order four-domain model for the WHOQOL-100.



These parameter estimates show that in case of Physical Health, facet 10 (Activities of Daily Living) and Facet 2 (Energy and Fatigue) had the highest loadings.

For the other three domains, Psychological Health, Social Relationships, and Environment, the highest regression weights were, respectively: Facet 4 (Positive Feelings), Facet 13 (Personal Relationships), and Facet 20 (New Information/Skills)

Construct validity

The EORTC- QLQ BR 23, CES-D and STAI (T2) scores were correlated with the 25 facets and the four domains of the WHOQOL-100 in the BC group. The results are presented in Table 4. Only significant correlations (2-tailed tested) are reported. In accordance with our expectations, scores on the EORTC QLQ-BR23, the CES-D, and the STAI-state scale correlated highly (r >.49) with related facets of the WHOQOL-100. For instance, the EORTC-QLQ-BR23 scale Body Image was highly correlated with the WHOQOL-100 facet Body Image and Appearance. The EORTC-QLQ-BR23 scales Sexual Functioning and Sexual Enjoyment (EORTC-QLQ) were highly correlated with the WHOQOL-100 facet Sexual Activity. The EORTC-QLQ-BR23 facets Breast Symptoms and Arm Symptoms were predominantly correlated with facets in the Physical Health domain of the WHOQOL-100. Much lower correlations (r < .29) were found between, for example, the WHOQOL-100 facets Financial Resources and Transport, on the one hand, and EORTC QLQ-BR 23 dimensions, on the other hand. Finally, the global QOL/General Health facet demonstrated low to moderate associations with the related EORTC QLQ BR-23 dimensions. The EORTC-QLQ-BR scale Future Prospective was most strongly correlated with the global QOL/General Health facet of the WHOQOL-100.

Table 4. Construct validity of the WHOQOL-100 (BC group)

WHOQOL-100 facets	EORTC-QLQ-BR23								CESD	STAI
	BI	SF	SE	FP	SS	BS	AS	HL		
Overall QOL/General Health	**.22**			.48	**-.26**				-.64	-.63
Physical Health		.35		.46	-.28	-.40	-.51		-.60	-.50
Pain and discomfort	**-.21**			-.44		.44	.45		.56	.47
Energy and fatigue					.37	-.31	-.38	**-.28**	-.53	-.39
Sleep and rest					.31		-.16	-.34	-.45	-.45
Mobility		.37		.28			-.45		-.35	-.34
Activities of daily living		**.31**		.39	.27	-.52	-.42		-.50	-.36
Dependence/medication				-.27				**.25**	.38	.31
Working capacity		.27		.32	**-.21**	-.30	-.46	**.61**	-.38	-.27
Psychological Health	.29	**.26**		.41					-.67	-.70
Positive feelings		**.29**		.41					-.66	-.69
Cognitive functions		**.24**		.33					-.49	-.55
Self-esteem		**.29**		.26					-.53	-.56
Body image/appearance	.58				**-.24**	**-.22**			-.50	-.36
Negative feeling	-.29			-.60					.77	.71
Spirituality/religion/ Personal beliefs										
Social Relationships		.40		.37					-.54	-.56
Personal relationships		**.27**		.37					-.57	-.57
Social support		**.25**		.32			**-.25**		-.48	-.46
Sexual activity		.50		**.23**					-.36	-.43
Environment		**.30**		**.25**					-.33	-.44
Physical safety/security		**.24**		**.26**	-.31				-.39	-.46
Home environment				**.23**					-.32	-.37
Financial resources										
Health and social care										-.30
New information/skills				.26					**-.22**	-.39
Participation recreation		.33		.36			**-.25**		-.56	-.63
Physical environment				**.21**				.65	**-.25**	**-.21**
Transport						**-.21**		**.64**		

Abbreviations: BI =Body Image, SF = Sexual Functioning, SE = Sexual Enjoyment, FP = Future Perspective, SS = Systemic therapy Side effects, BS = Breast Symptoms, AS = Arm Symptoms, HL = upset by Hair Loss.

Note: Non-significant results are not shown. All correlations are significant at 0.01 (2-tailed tested), except for the correlations in bold (significant at 0.05; 2-tailed tested). The relatively high associations between HL and Working Capacity, Physical Environment, and Transport are probably due to small number of participants who filled in this subscale (n≈25)

Table 5. Construct validity of the WHOQOL-100 (BCS group)

WHOQOL- 100 facets	SF-36									CESD	STAI
	GH	PF	SF	RLF	RLM	MH	V	BP	HC		
Overall QOL/General Health	.65	.45	.54	.51	.43	.60	.57	.51	.29	-.48	-.56
Physical Health	.70	.53	.62	.67	.39	.55	.71	.64	.25	-.58	-.49
Pain and discomfort	-.60	-.36	-.50	-.48	-.33	-.52	-.60	-.68	-.22	.48	.40
Energy and fatigue	.59	.49	.60	.64	.35	.60	.83	.56	**.21**	-.59	-.49
Sleep and rest	**.20**		.34	**.20**	**.21**	.35	.33	.24		-.31	-.31
Mobility	.39	.34	.31	.39	.24	.34	.40	.37	**.19**	-.28	-.24
Activities of daily living	.72	.59	.61	.71	.41	.51	.60	.63	.23	-.57	-.44
Dependence/medication	-.58	-.42	-.41	-.40	-.34	-.35	-.40	-.51		.37	..34
Working capacity	.65	.47	.61	.67	.42	.44	.54	.51	**.19**	-.58	-.41
Psychological Health	.49	.32	.43	.43	.36	.69	.57	.41	.25	-.63	-.62
Positive feelings	.46	.30	.37	.37	.36	.47	.43	.33		-.56	-.52
Cognitive functions	.35	**.17**	.30	.25		.38	.40	.31	**.19**	-.37	-.32
Self-esteem	.35	.24	.23	.32	**.19**	.50	.35	.35	**.21**	-.44	-.42
Body image/appearance	**.22**	**.17**	**.21**	**.20**	.26	.39	.30	**.19**		-.30	-.31
Negative feeling	-.47	-.29	-.51	-.44	-.41	-.71	-.52	-.40	**-.21**	-.63	-.62
Spirituality/religion/personal Beliefs											
Social Relationships	.23		.24	.23		.24	.26			-.35	.34
Personal relationships	.32	**.20**	.31	.24	**.19**	.39	.34	.32		-.47	-.47
Social support	.23					**.18**	**.22**			-.23	-.29
Sexual activity	.28	**.18**	.26	.30	**.20**	.34	.30	**.22**		-.42	-.30
Environment	.42	.39	.42	.41	.35	.36	.43	.32		-.43	-.43
Physical safety/security	.23		.24	**.18**		.30	.26		**.17**	-.30	-.32
Home environment	.23	**.21**		.22		**.19**	.24			-.23	-.28
Financial resources	.26	.25	.30	.26	**.21**	**.21**	.28	.22		-.28	-.27
Health and social care	.22		**.19**				**.20**	**.19**			
New information/skills	.43	.35	.33	.34	.30	.32	.41	.31		-.40	-.41
Participation recreation	.39	.32	.47	.43	.37	.51	.44	.34	.30	-.54	-.55
Physical environment	**.19**					.22	**.20**	**.20**		-.30	**-.19**
Transport	.34	.45	.38	38	.32	.20	.40	.27			

Abbreviations: GH = General Health, PF = Physical Functioning, SF = Social Functioning, RLF = Role Limitations Physical, RLM = Role Limitations Mental, MH = Mental Health, V = Energy / fatigue, BP = Bodily Pain, HC = Health Changes

Note: Non-significant results are not shown. All correlations are significant at 0.01 (2-tailed tested), except for the correlations in bold (significant at 0.05; 2-tailed tested).

The CES-D and STAI-state correlated significantly with all domains and facets of the WHOQOL-100, except for the WHOQOL-100 facets Spirituality, Religion and Personal Beliefs, Financial Resources, and Transport.

The SF-36, CES-D and STAI scores were correlated with the domains and facets of the WHOQOL-100 in the BCS group. The results are presented in Table 5. Related subscales of the SF-36 were highly correlated with the WHOQOL-100 domains and facets, while low correlations were found between non-related domains and facets. For instance, the SF-36 subscales General Health and Physical Functioning were highly correlated with the WHOQOL-100 Physical Domain. Low correlations were found between the SF-36 Bodily Pain and the WHOQOL-100 Financial Resources.

Reliability

Cronbach's alpha coefficients were calculated separately for the BBP group, the BC group, and the BCS group (See Table 6). In all groups, all alpha coefficients exceeded .70. In the BC group, they ranged for the domains from .76 (Social Relationships) to .88 (Environment). The alpha coefficients in the BBP group ranged from .78 (Social Relationships) to .91 (Physical Health). At the facet level, the internal consistency exceeded .72 for all facets in all groups.

Table 7 presents test-retest correlations. Correlations were all strong and significant at the 0.01 level (2-tailed tested), ranging from .58 (Self-esteem) to .90 (Financial Resources).

Table 6. Internal consistency

WHOQOL-100 domains and facets	Cronbach's alpha[1]		
	BBP (T2)	BC (T2)	BCS
Overall QOL and General Health	.88	.87	.87
Physical Health	**.91***	**.85***	**.85***
Pain and discomfort	.77	.77	.87
Energy and fatigue	.90	.91	.88
Sleep and rest	.93	.92	.91
Mobility	.90	.91	.92
Activities of daily living	.91	.90	.90
Dependence/medication	.92	.85	.87
Working capacity	.94	.94	.87
Psychological Health	**.83***	**.84***	**.68***
Positive feelings	.81	.82	.77
Cognitive functions	.82	.84	.81
Self-esteem	.83	.84	.74
Body image and appearance	.91	.99	.84
Negative feelings	.85	.86	.81
Spirituality/religion/personal beliefs	.92	.90	.73
Social Relationships	**.78***	**.76***	**.71***
Personal relationships	.74	.78	.57
Social support	.89	.88	.80
Sexual activity	.82	.82	.86
Environment	**.85***	**.88***	**.83***
Physical safety and security	.72	.78	.68
Home environment	.75	.74	.74
Financial resources	.93	.91	.87
Health and social care	.81	.84	.80
Opportunities for New Information and Skills	.84	.84	.84
Participation recreation	.81	.80	.74
Physical environment	.72	.75	.66
Transport	.92	.92	.88

[1] Cronbach's alpha coefficients were calculated at item level, except for the values marked with *, which were calculated at facet level.

Table 7. Test-retest correlations T2 en T3 (BBP group)

WHOQOL-100	
Domains and facets	Correlations (r)
Overall QOL and General Health	.85
Physical Health	.92
Pain and discomfort	.73
Energy and fatigue	.85
Mobility	.83
Activities of daily living	.81
Dependence/medication	.87
Working capacity	.84
Psychological Health	.91
Positive feelings	.84
Cognitive functions	.83
Self-esteem	.58
Body image and appearance	.87
Negative feelings	.84
Spirituality/religion/personal beliefs	.72
Social Relationships	.86
Personal relationships	.81
Social support	.81
Sexual activity	.77
Environment	.85
Physical safety and security	.77
Home environment	.79
Financial resources	.90
Health and social care	.69
Opportunities for new information and skills	.73
Participation recreation	.82
Physical environment	.77
Transport	.85

Note: All correlations (Pearson r product-moment correlations) were significant at the 0.01 level (2-tailed tested).

Discussion

The aim of the present study was to examine the psychometric properties of the WHOQOL-100 in a population of women with breast abnormalities (benign or malignant) and breast cancer survivors. Before examining the reliability and validity of the WHOQOL-100, confirmatory factor analyses (CFA) were conducted to test whether the original six-domain structure and the in more recent publications suggested four-domain structure were suited to a population with (former) breast problems. Both models fitted well, although in both cases some modification in specification was needed in order to determine a model that better represented the sample data. In case of both models some measurement error covariances appeared to be systematic rather than random. It is difficult to indicate whether they derive predominantly from item characteristics (e.g., a high degree of overlap in item content), or respondent characteristics (e.g., response bias), or interactions between item and respondent features. The four-domain model, however, demonstrated to a lesser extent such possible areas of misfit. Therefore, we prefer the four-domain structure and conclude that the WHOQOL-100 is a truly generic instrument, which is also applicable to women with breast problems.

The WHOQOL-100 seemed to be a reliable instrument for the use in women with breast problems. That is, the internal consistencies were more than satisfactory, with all Cronbach's alpha coefficients exceeding .70 for all domains and facets, demonstrating homogeneity of item content. This is consistent with the finding of Tazaki et al. [22] who also reported an adequate Cronbach's alpha for the total scale. Test-retest reliability was high.

With regard to validity, we expected that the WHOQOL-100 would correlate moderately with related components of the EORTC – QLQ BR 23 and the CES-D. The associations that were found between the WHOQOL-100 and the other instruments confirmed the hypothesis regarding the EORTC-QLQ-BR 23 scale Body Image, high correlations were found with the WHOQOL-100 facet Body Image and Appearance. The global WHOQOL-100 facet correlated most strongly with the EORTC-QLQ-BR 23 scale Future Prospective. In addition, the CES-D, and STAI-state correlated significantly with all domains and facets of the WHOQOL-100. Pearson correlations between both questionnaires ranged

between -.21 and .77. The highest correlation between the WHOQOL-100 and the EORTC-QLC-BR23 was .65 for QOL Physical Environment and HS Upset by Hair Loss, indicating that outcome measures are not interchangeable. Other studies also indicated that QOL and HS are distinct concepts [41-43].

A limitation of the present is study is that women with breast problems (BBP and BC) were asked to participate and to fill in questionnaires, while they were under great stress. Therefore, we needed several groups in order to establish the psychometric evidence for the WHOQOL-100. For instance, test-retest reliability was checked in relatively stable persons (BBP) at T2.

In conclusion, the results of the present study showed that the WHOQOL-100 had good reliability and validity, and, therefore, is a suitable instrument for measuring QOL in a population of women who have (had) abnormalities (benign or malignant) of the breast.

References

1. McPherson K, Steel CM, Dixon JM. ABC of breast diseases: breast cancer---epidemiology, risk factors, and genetics. BMJ 2000;321:624-628.
2. Europäische Kommission [European Comittee]. Die Gesundheitssituation in der Europäischen Union (The health situation in the European Union). Amt fur amtliche Veröffentlichungen der Europäischen Gemeinschaften. Luxemburg; 2003.
3. Poortmans PMP. Quality assurance in clinical trials in breast cancers. Herentals, België: Drukkerij Bulckens NV; 2005.
4. Coebergh JWW, Janssen-Heijnen MLG, Voogd AC, Louwman WJ, editors. Cancer: incidence, care and survival in the south of the Netherlands. Eindhoven, The Netherlands: Comprehensive Cancer Centre South (IKZ); 2001.
5. Gallagher J, Parle M, Cairns D. Appraisal and psychological distress six months after diagnosis of breast cancer. Br J Health Psychol 2002;7:365-376.
6. Alfano CM, McGregor BA, Kuniyuki A, Reeve BB, Bowen DJ, Wilder Smith A, et al. Psychometric evaluation of the Brief Cancer Impact Assessment among breast cancer survivors. Oncology 2006;70:190-202.
7. Ware JE. SF-36 Health Survey: manual & interpretation guide. Boston, MA: The Health Institute, New England Medical Center; 1993.
8. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-376.
9. Sprangers MA, Groenvold M, Arraras JI, Franklin J, Te Velde A, Muller M, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996;14:2756-2768.
10. De Vries J. Assessment in behavioural medicine. In: Vingerhoets AJJM, editor. Quality of life assessment. Hove, UK: Brunner-Routledge, 2001. p. 353-370.

11. Van der Steeg AF, De Vries J, Roukema JA. Quality of life and health status in breast carcinoma. Eur J Surg Oncol 2004;30:1051-1057.
12. Suurmeijer TP, Reuvekamp MF, Aldenkamp BP. Social functioning, psychological functioning, and quality of life in epilepsy. Epilepsia 2001;42:1160-1168.
13. Moons P, Budts W, De Geest S. Critique on the conceptualisation of quality of life: a review and evaluation of different conceptual approaches. Int J Nurs Stud 2006;43:891-901.
14. WHOQOL Group. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc Sci Med 1998;46:1569-1585.
15. WHOQOL group. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med 1995;41:1403-1409.
16. Andrykowski MA, Curran SL, Studts JL, Cunningham L, Carpenter JS, McGrath PC, et al. Psychosocial adjustment and quality of life in women with breast cancer and benign breast problems: a controlled comparison. J Clin Epidemiol 1996;49:827-834.
17. Cordova MJ, Cunningham LL, Carlson CR, Andrykowski MA. Posttraumatic growth following breast cancer: a controlled comparison study. Health Psychol 2001;20:176-185.
18. O'Carroll RE, Smith K, Couston M, Cossar JA, Hayes PC. A comparison of the WHOQOL-100 and the WHOQOL-BREF in detecting change in quality of life following liver transplantation. Qual Life Res 2000;9:121-124.
19. O'Carroll RE, Couston M, Cossar J, Masterton G, Hayes PC. Psychological outcome and quality of life following liver transplantation: a prospective, national, single-center study. Liver Transpl 2003;9:712-20.
20. Skevington SM, Carse MS, Williams AC. Validation of the WHOQOL-100: pain management improves quality of life for chronic pain patients. Clin J Pain 2001;17:264-275.
21. Masthoff ED, Trompenaars FJ, Van Heck GL, Hodiamont PP, De Vries J. Validation of the WHO Quality of Life assessment instrument

(WHOQOL-100) in a population of Dutch adult psychiatric outpatients. Eur Psychiatry 2005;20:465-473.

22. Tazaki M, Nakane Y, Endo T, Kakikawa F, Kano K, Kawano H, et al. Results of a qualitative and field study using the WHOQOL instrument for cancer patients. Jpn J Clin Oncol 1998;28:134-141.
23. Power M, Harper A, Bullinger M. The World Health Organization WHOQOL-100: Tests of the universality of Quality of Life in 15 different cultural groups worldwide. Health Psychol 1999;18:495-505.
24. Lampic C, Thurfjell E, Sjoden PO. The influence of a false-positive mammogram on a woman's subsequent behaviour for detecting breast cancer. Eur J Cancer 2003;39:1730-1737.
25. Spielberger CD, Gorsuch RL, Lushene RE. STAI manual for the State-Trait Anxiety Inventory. Palo-Alto, CA: Consulting Psychologists Press; 1970.
26. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385-401.
27. De Vries J, Van Heck GL. The World Health Organization Quality of Life assessment instrument (WHOQOL-100): validation study with the Dutch version. Eur J Psychol Assess 1997;13:164-178.
28. WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med 1998;28:551-558.
29. Sprangers MA, Cull A, Bjordal K, Groenvold M, Aaronson NK. The European Organization for Research and Treatment of Cancer. Approach to quality of life assessment: guidelines for developing questionnaire modules. EORTC Study Group on Quality of Life. Qual Life Res 1993;2:287-295.
30. Yun YH, Bae SH, Kang IO, Shin KH, Lee R, Kwon SI, et al. Cross-cultural application of the Korean version of the European Organization for Research and Treatment of Cancer (EORTC) Breast-Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23). Support Care Cancer 2004;12:441-445.
31. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch

language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055-1068.

32. Van der Ploeg HM, Defares PB, Spielberger CD. ZBV: a Dutch-language adaptation of the Spielberger State-Trait Anxiety Inventory. Lisse, The Netherlands: Swets & Zeitlinger; 1980.
33. De Rijk AE, Schreurs KMG, Bensing JM. What is behind "I'm so tired"? Fatigue experiences and their relations to the quality and quantity of external stimulation. J Psychosom Res 1999;47:509-523.
34. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. Psychol Med 1997;27:231-235.
35. Oh S, Heflin L, Meyerowitz BE, Desmond KA, Rowland JH, Ganz PA. Quality of life of breast cancer survivors after a recurrence: a follow-up study. Breast Cancer Res Treat 2004;87:45-57.
36. Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct Equ Model 1999;6:1-55.
37. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum; 1988.
38. Cohen J. Statistical power analysis for the behavioural sciences. New York, NY: Wiley; 1977.
39. Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika 1951;16:297-334.
40. Arbuckle JL. Amos 6.0 [statistical program]. In. Chicago, IL: SPSS; 2005.
41. Breek JC, De Vries J, Van Heck GL, Van Berge Henegouwen DP, Hamming JF. Assessment of disease impact in patients with intermittent claudication: discrepancy between health status and quality of life. J Vasc Surg 2005;41:443-450.
42. O'Carroll RE, Cossar JA, Couston MC, Hayes PC. Sensitivity to change following liver transplantation: a comparison of three instruments that measure quality of life. J Health Psychol 2000;5:69-74.

43. Huang IC, Wu AW, Frangakis C. Do the SF-36 and WHOQOL-BREF measure the same constructs? Evidence from the Taiwan population. Qual Life Res 2006;15:15-24.

Chapter 3

Predictors of overall quality of life in women with early stage breast cancer: which quality of life domains and facets weight most?*

* Den Oudsten BL, De Vries J, Van der Steeg AFW, Roukema JA, Van Heck GL. Predictors of overall quality of life in women with early stage breast cancer: which quality of life domains and facets weight most? (Submitted for publication).

Abstract

Objective: Scores on quality of life (QOL) domains and facets are probably subject to fluctuations across time due to the course of breast cancer (BC) treatment. Existing QOL studies have been cross-sectional. Therefore, this prospective follow-up study is the first to examine whether QOL domains (physical health, psychological health, social relationships, and environment) and QOL facets contributed differentially across time to overall QOL in women with early stage BC. *Methods*: From the 608 participating women, 225 women had early stage BC. Before diagnosis (Time-1) and one (Time-2), three (Time-3), six (Time-4), and 12 months (Time-5) after surgical treatment, women with early stage BC were assessed on QOL (WHOQOL-100). *Results*: Psychological Health and Social Relationships were the QOL-domains that predicted overall QOL most consistently at the various time points. Environment contributed to a lesser extent to overall QOL compared with Physical Health, Psychological Health, and Social Relationships. Almost at all measurement points, the facets Positive Feelings and Personal Relationships were important factors in the process of maintaining a good overall QOL. *Conclusions*: QOL domains and facets contributed differently to overall QOL at various time points across treatment in women with early stage BC.

Introduction

In the Netherlands, over 11,500 women were diagnosed with breast cancer (BC) in 2003 [1]. In 2005, there were an estimated number of 119,000 BC patients or BC survivors in the Netherlands. Due to advances in cancer screening and medical treatment, this number might increase to about 194,000 within ten years [2]. In recent decades, breast conserving therapy has become an alternative to mastectomy. Most women with early stage BC have a choice between these two treatment options, which have equivalent survival rates [3, 4]. However, this decision is not easy to make. Therefore, concepts like quality of life (QOL) are important because they can inform surgeons and patients in the decision-making process of determining which treatment options to use [5].

In general, definitions of QOL emphasize that QOL is multidimensional [6] and in the eye of the beholder [7]. QOL represents subjective evaluations of oneself, one's social and material world, and reflects the extent to which the individual is satisfied with them or is bothered by problems in those areas [7]. In line with this principle, the World Health Organization Quality of Life Group (WHOQOL Group) defined QOL as "an individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards and concerns. It is a broad-ranging concept incorporating in a complex way the person's physical health, psychological state, level of independence, social relationships, personal beliefs and relationship to salient features of the environment" (p. 1405) [8]. In line with this conceptualization, the WHOQOL Group has developed the WHOQOL-100 instrument. This questionnaire assesses three levels of QOL: (i) the first level corresponds with overall QOL, (ii) the second level consists of the separate domains of QOL, and (iii) the third level is formed by the specific aspects within each domain. This approach is consistent with Spilker's hierarchical model of QOL [9]. Moreover, Spilker's model assumes that QOL variables at a lower level determine QOL variables at a higher level. This "pyramid model" containing lower and higher QOL levels has practical relevance because it gives insight in the consequences of an illness for patients in terms of valuation of life [10].

Few studies have examined the contribution of physical, psychological, and social well-being to patient's evaluations of overall QOL [10-12]. One study found that the domain of psychological functioning contributed to overall QOL in healthy subjects as well as patients with chronic disorders [11]. However, this study did not include breast cancer patients. Another study described the role of fatigue and QOL domains on overall QOL in lung and breast cancer patients preceding radiotherapy [10]. These studies have major limitations because of small sample size, the employment of a cross-sectional design, and the assessment of the first and second level of QOL only. Little research has been conducted to assess quantitatively the relationships between QOL domains in breast cancer patients [10]. Differences in the contribution of specific QOL domains and QOL facets can be expected between different diseases [10]. However, differences can also be expected across time. According to Leventhal and Colman [13], there is a "need to assess the importance assigned to various experiential domains in making quality of life judgments, and the need to understand that people observe, and then integrate, experienced events into quality of life judgments" (p.758). Recently, Lu et al. [14] stated that it is important to acquire detailed information regarding the contributions of separate domains and facets of QOL to overall QOL judgments. It is quite conceivable that the salience, meaning, and importance of the domains and their consistent facets as well as the ways they are integrated will change over time.

To the best of our knowledge, the present prospective follow-up study is the first to examine the relationships between QOL domains (second level: Physical Health, Psychological Health, Social Relationships, and Environment) and facets (third level), on the one hand, and overall QOL (first level), on the other hand, at several moment in time in women with early stage BC. In addition, this study examined which baseline assessments of QOL domains and facets contributed substantially to overall QOL at one-year after surgical treatment. From a theoretical point of view, knowledge about the relationships between lower level assessment of QOL and higher level assessment is important, since it provides insight in the process underlying overall QOL judgments [11]. Moreover, as several clinicians and researchers prefer to use composite scores in QOL assessments in clinical practice, we now gain a better understanding of the usefulness of this preference for combining subtest scores. For instance, "it is the

patient's view of the disease and its treatment, and his or her view as to how they affect the physical, psychological, and social self, that holds the key to understanding quality of life" (p.670) [13]. We hypothesized that the association between different QOL-domains and facets, on the one hand, and overall QOL, on the other hand, in early stage BC patients would differ across time. For instance, facets of physical health and social relationships were expected to be more important during the first months after surgical treatment, while it is quite conceivable that facets of psychological health would be rated as most important in later time periods. Furthermore, we hypothesized that the Environment-domain would contribute to a lesser extent to the prediction of overall QOL compared with Physical Health, Psychological Health, and Social Relationships. Finally, it was expected that facet scores belonging to the domains of Social Relationships and Psychological Health assessed at baseline, would play a significant role in the prediction of overall QOL one-year after surgical treatment.

Method

Participants

Women with a palpable lump in the breast or an abnormality on a screening mammography were referred by their general practitioner to the surgical outpatient clinics of the St. Elisabeth Hospital (Tilburg, The Netherlands), the Maasland Hospital (Sittard, The Netherlands), or the Jeroen Bosch Hospital (Den Bosch, The Netherlands). The present study, in which the predictors of overall QOL are examined, is part of a larger prospective follow-up study focusing on the role of personality in early stage BC patients' QOL.

The data were collected from September 2002 until September 2006. Of the 799 eligible women, 609 (76.2%) completed the first set of questionnaires before diagnosis was known. The main reasons for not participating were the length of questionnaires and the amount of stress women experienced at their first visit at the hospital. Of these 609 women, 223 were subsequently diagnosed with early stage breast cancer (BC). Women who had a history of abnormalities in the breast, benign or malignant, or had a breast tumor that was too large (>5 centimeter) for breast conserving therapy, were excluded from the study. In order to participate, the women had to be able to write and read in Dutch. The questionnaires were completed before the women visited the surgeon and

radiologist, i.e. before the diagnosis, benign or malignant, was known. After the baseline measurement (Time-1), women completed questionnaires at one (Time-2), three (Time-3), six (Time-4), and 12 (Time-5) months after surgical treatment. The reference point was surgical treatment because otherwise follow-up measures would interfere with the timing of treatment modalities. Participation in the study was not known to the surgeon in attendance and, therefore, did not affect treatment and clinical follow-up. All participants gave written informed consent.

Measurements

QOL was measured at all time points using the WHOQOL-100 [15, 16], a cross-culturally developed generic multidimensional instrument. This instrument covers 24 facets, assessed with 96 questions, and one General Health and Overall Quality of Life facet (4 questions). In this study, we used this General Health and Overall Quality of Life facet as the dependent variable. Because this scale also included one item on general health, we decided to exclude this particular item from the analysis. Each facet of the WHOQOL-100 is measured with four items using a 5-point Likert scale. The 24 facets were initially scored in six domains of QOL: Physical Health, Psychological Health, Levels of Independence, Social Relationships, Environment, and Spirituality, Religion and Personal Beliefs [15]. Nowadays, it is well accepted to convert these 24 facets into four domains as described by the WHOQOL group [17-19]. In general high facet scores indicate good QOL, except for Pain and Discomfort, Negative Feelings, and Dependence on Medication or Treatments. The time frame of reference is the previous two weeks. Reliability and validity [16, 17, 19] are adequate, and sensitivity [20] is high. Recently, the WHOQOL-100 is validated in a group of BC patients, women with benign breast problems, and BC survivors [19]. Cronbach's alpha coefficients ranged for the domains from .76 (Social Relationships) to .88 (Environment) in the BC group. At the facet level, the internal consistency exceeded .72 for all facets in all groups [19].

Socio-demographic and clinical variables

Information on sociodemographic data (age, partner status, educational background, and employment status) was obtained by self-report at Time-1.

Clinical information (diagnosis, disease stage, type of surgery, tumor size, adjuvant therapy) was obtained from the medical files.

Statistical procedure

Student *t*-tests and Chi-square tests were used to examine the potential differences between participants and non-participants. Multiple linear regression analyses (method: enter) were used to examine the associations of QOL domains and facets, on the one hand, and overall QOL at the various time points, on the other hand (Time-2 to Time-5). In order to preserve statistical power, two preliminary multiple linear regression analyses were run. First, we determined which QOL domains (Physical Health, Psychological Health, Social Relationships, Environment) were significantly associated with overall QOL at a given time point. Second, those QOL facets of a significant contributing domain were entered in a subsequent regression analysis. For instance, if Psychological Health (Time-2) was associated with overall QOL (Time-2), the facets belonging to that particular domain (Positive Feelings, Cognitive Functions, Self-esteem, Body Image and Appearance, Negative Feelings, and Spirituality Religion Personal Beliefs) were entered in the regression analysis. Thus, dependent and independent variables entered in the regression analyses were measured at the same time point. The final analysis included all facets that were significantly associated with overall QOL for a given time point. In order to determine whether QOL domains and facets assessed at baseline predict overall QOL at Time-5, multiple linear analyses were used. Again, preliminary analyses were used (as described above). However, different time points were now used. Statistical significance was designated at a *p*-value of .05 or smaller. In addition, we examined which QOL facets as measured at Time-1 predicted overall QOL at Time-5. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Chicago, IL, USA; version 14.0).

Results

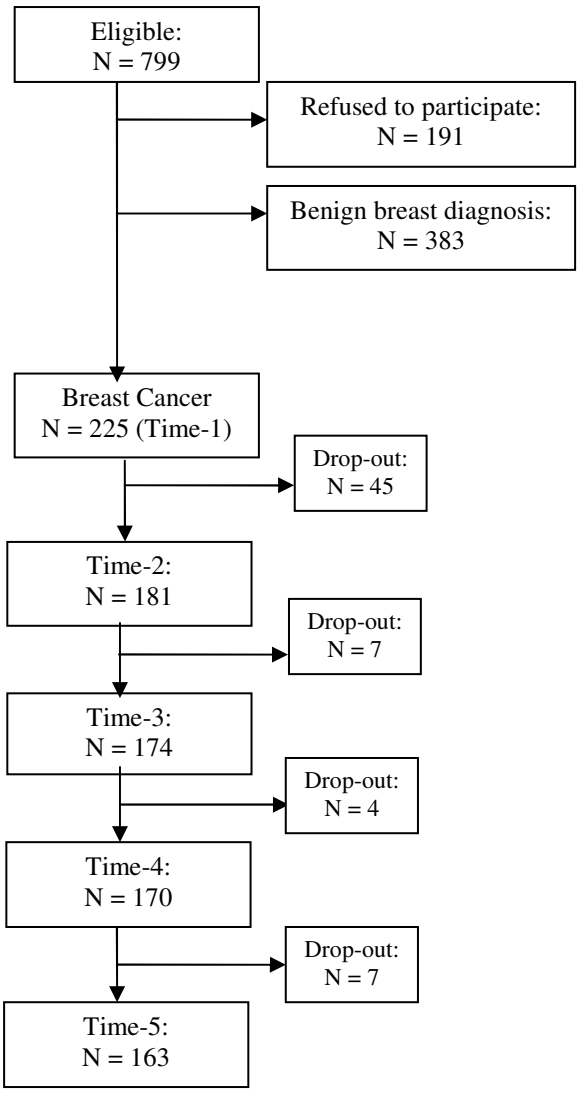
Demographic and clinical characteristics are presented in Table 1. Participants were significantly younger than non-participants (p =.002). They did not differ on other sociodemographic or clinical characteristics. Figure 1 presents the flow chart of this study.

Table 1. Socio-demographic and characteristics of the participants at baseline

	BC group (n = 225)
Age at diagnosis (mean ± SD)	58.7 (9.4)
Living with a partner (yes/no/missing)	180 (80.3) / 38 (16.6) / 7 (3.1)
Having children (yes/no/missing)	191 (84.9) 29 (13.1) / 3 (1.3)
Educational level	86 (38.2) / 95 (42.2) / 38 (16.9) / (4.0)
(0-9 yrs / 10-14 yrs / >14 years /missing)	
Paid work (yes/no/missing)	86 (38.2) / 136 (60.4) / 3 (1.3)
Diameter of tumor	
<1 cm / 1-3 cm / >3 cm	49 (22.0) / 146 (65.5) / 25 (11.2)
Type of surgery	
BCT/ MTC/ No surgical treatment	106 (47.1) / 115 (51.1) / 4 (1.8)
Adjuvant therapy	
Yes / No	171 (75.9) / 54 (24.1)
Disease stage	
Stage 0	26 (11.6)
Stage I	92 (40.9)
Stage IIa	68 (30.2)
Stage IIb	35 (15.6)
Indefinable	2 (0.9)

Abbreviations: MTC = modified radical mastectomy; BCT = breast conserving therapy;
Note: For the socio-demographics, percentages are between brackets (except for age).

Figure 1. Flow chart of participants



Associations between QOL domains and overall QOL

Preliminary analysis showed that the Physical Health-domain (only Time-2) and Environment-domain (only Time-3 and Time-5) did not significantly contribute to overall QOL. Therefore, facets belonging to Physical Health and Environment were left out of further analyses at these time points (Table 2). At all time points, overall QOL was associated with the domains Psychological Health and Social Relationships. Compared with the Physical Health domain and Social Relationships domain, the facets of the Psychological Health-domain explained the largest proportion of variance in the association with overall QOL across time (adjusted $R^2 > .63$).

Facets belonging to the physical domain, for instance, Sleep and Rest, Mobility, Activities of Daily Living, and Working capacity turned out to be relevant at some point(s) in time. The facets Sleep and Rest and Mobility, for instance, predicted overall QOL especially in the first month after surgical treatment, while Working Capacity became significantly associated with overall QOL one year after surgical treatment. This also applies for the facets Cognitive Functions, Self-esteem, and Negative Feelings (Psychological Health). However, the facet Positive Affect was significantly associated with overall QOL across al time points. All facets belonging to the Social Relationships domain were associated with overall QOL at some time points. However, Personal Relationships was positively associated with overall QOL across *all* time points. Several facets, for instance, Body Image and Appearance and Spirituality Religion Personal Beliefs, were not significantly associated with overall QOL throughout all analyses (Table 3).

Table 2. Beta weights for preliminary multivariate regression analyses of overall QOL after surgical treatment

Predictor variables QOL domains (level 2)	Time-2	Time-3	Time-4	Time-5
Physical Health	.09 ns	.27 ***	.20 **	.16 *
Psychological Health	.46 ***	.42 ***	.35 ***	.45 ***
Social Relationships	.26 ***	.22 ***	.28 ***	.23 **
Environment	.15*	.07 ns	.17 **	.14 ns

Note: *** $p<.0001$, ** $p < .001$, * $p < .05$, ns = not significant

Table 3. Beta weights for preliminary multivariate regression analyses of overall QOL after surgical treatment

Predictor variables QOL facets (level 3)	Time-2	Time-3	Time-4	Time-5
Physical Health				
Pain and Discomfort		-.04 ns	-.16 ns	-.14 ns
Energy and Fatigue		.18 ns	.07 ns	-.13 ns
Sleep and Rest		.19 **	.10 ns	.13 ns
Mobility		.26 **	.13 ns	.14 ns
Activities of Daily Living		.23 ns	.28 *	.28 *
Dependence of Medication		.04 ns	-.11 ns	-.01 ns
Working Capacity		-.00 ns	-.00 ns	.27 *
Psychological Health				
Positive Feelings	.25 **	.30 ***	.40 ***	.47 ***
Cognitive Functions	.14 ns	.16 *	.23 **	.24 ***
Self-esteem	.27 **	.18 ns	.19 *	.13 ns
Body Image and Appearance	.02 ns	.09 ns	.04 ns	.04 ns
Negative Feelings	-.20 **	-.19 **	-.08 ns	-.12 ns
Spirituality, Religion, Personal Beliefs	.10 ns	.09 ns	.03 ns	.06 ns
Social Relationships				
Personal Relationships	.62 ***	.54 ***	.43 ***	.54 ***
Social Support	.07 ns	.10 ns	.30 ***	.14 ns
Sexual Activity	.12 ns	.16 *	.17 **	.15 *
Environment				
Physical Safety and Security	.17 *		.22 *	
Home Environment	.12 ns		.12 ns	
Financial Resources	.00 ns		.04 ns	
Health and Social Care	.02 ns		.13 ns	
Opportunity for Acquiring Skills	.12 ns		-.08 ns	
Participation in Leisure	.57 ***		.49 ***	
Physical Environment	-.16 *		-.02 ns	
Transport	-.10 ns		.00 ns	

Note: *** p<.0001, ** p < .001, * p < .05, ns = not significant

In the final analyses, the most consistent facets contributing to overall QOL were Positive Feelings and Personal Relationships. Other facets, for instance, Self-esteem (Time-2) and Cognitive Functioning (Time-3), contributed only once to the prediction of overall QOL. Table 4 presents the standardized beta weights, confidence intervals, ANOVAs and Adjusted R^2 for the multivariate regression analyses.

Predictors of overall QOL

Preliminary analyses showed that the domains Physical Health (β = .24, p < .0001), Psychological Health (β = .13, p = .037), Social Relationships (β = .19, p= .001), and Environment (β = .22, p < .0001), assessed at baseline (Time-1), contributed significantly to overall QOL (Time-5). The Physical Health facets Sleep and Rest (β = .14, p = .006) and Mobility (β = .15, p = .014) predicted overall QOL at Time-5. Positive Affect (β = .18, p = .004), Cognitive Functioning (β = .18, p < .003), and Self-esteem (β = .25, p < .0001) belonging to the Psychological Health domain predicted overall QOL at Time-5. Personal Relationships (β = .38, p < .0001) and Sexual Activity (β = .19, p < .0001) were significantly associated with overall QOL. Finally, the facets Health and Social Care (β = .15, p = .009), Opportunity for Acquiring Skills (β = .15, p = .021), and Participation in Leisure (β = .25, p < .0001) predicted overall QOL.

The final analysis showed that: Mobility (β = .17, p < .0001), Personal Relationships (β = .19, p = .003), Sexual Activity (β = .12, p = .013), and Opportunity for Acquiring Skills (β = .13, p = .038) were significantly contributing to the prediction of overall QOL, explaining 44.4% of the variance (Adjusted R^2).

Table 4. Final multivariate linear regression analyses

	Predictor variables QOL facets (level 3)	ß	*p*-value	
Time-2	Positive Feelings	.15	ns	$F = 42.48$***
	Self-esteem	.17	.046	
	Negative Feelings	-.12	ns	Adjusted $R^2 = .67$
	Personal Relationships	.30	<.0001	
	Physical Safety	.08	ns	
	Participation in Leisure	.21	.012	
	Physical Environment	-.09	ns	
Time-3	Sleep and Rest	-.06	ns	$F = 51.11$***
	Mobility	.27	<.0001	
	Positive Feelings	.22	.004	Adjusted $R^2 = .66$
	Cognitive Functioning	.13	.047	
	Negative Feelings	-.13	ns	
	Personal Relationships	.32	<.0001	
	Sexual Activity	.02	ns	
Time-4	ADL	.16	.004	$F = 46.02$***
	Positive Feelings	.28	.001	
	Cognitive Functioning	.05	ns	Adjusted $R^2 = .74$
	Self-esteem	.11	ns	
	Personal Relationships	.01	ns	
	Social Support	.20	.001	
	Sexual Activity	.11	.038	
	Physical Safety	.17	.007	
	Participation in Leisure	.05	ns	
Time-5	ADL	.05	ns	$F = 46.02$***
	Working Capacity	.06	ns	
	Positive Feelings	.46	<.0001	Adjusted $R^2 = .68$
	Cognitive Functions	.02	ns	
	Personal Relationships	.32	<.0001	
	Sexual Activity	.07	ns	

Note: *** $p<.0001$, ns = not significant; *Abbreviations*: ADL, Activities of Daily Living

Discussion

The aim of this prospective follow-up study was to examine which QOL domains and facets contribute significantly to overall QOL in women with early stage BC during the first year after surgery. In this way, this study adds knowledge to our understanding of what determines the overall QOL scores of women with early stage BC.

Two domains of QOL, i.e., Psychological Health and Social Relationships, were significantly associated with overall QOL at all time points, which is in line with the findings of a previous cross-sectional study [11]. It was also found in the latter study that psychological functioning was important in people with a broad range of chronic diseases as well as in healthy subjects, while social functioning was contributing to overall QOL in only some of the chronic diseases (i.e., back problems, rheumatoid arthritis, and migraine). Thus, findings indicate that there may be differences between disease populations. As a consequence, future studies should examine the role of second and third level aspects in different samples.

Our hypothesis that different QOL facets would determine overall QOL at a given time point after BC diagnosis was partly confirmed. That is, two facets, namely Positive Feelings and Personal Relationships predicted overall QOL across all time points. However, other predictors did turn out to be relevant at some point(s) in time, except for the facet Body Image and Appearance. This factor remained non-significant throughout all analyses. This is in line with, for instance, Andritsch et al. [21] who found that body image did not play a substantial role after 1 to 5 years after BC diagnosis. Energy and Fatigue, Dependence on Medication, or Spirituality Religion Personal Beliefs predicted QOL the first month after diagnosis, while Working Capacity significantly predicted QOL 12 months after surgical treatment. Between 3 and 6 months, Sleep and Rest, and Sexual Activity contributed to the prediction of overall QOL. Facets belonging to the Psychological Domain were the predominant determinants of overall QOL in early stage BC. Physical Health contributed to a lesser extent to the explanation of overall QOL. This finding is in line with an earlier study [11].

The WHOQOL-100 contains a facet Overall QOL and Health consisting of four items. Three of these items refer to QOL, while the other item explicitly refers to how satisfied the individual is with his/her health. Therefore, in this study, we have used the three items that all explicitly refer to overall QOL. However, additional analysis showed that the results remained quite similar when the original facet Overall QOL and Health was used (results not shown), which is in line with earlier findings [10].

Knowledge about the factors contributing to overall QOL at a given time point will allow health professionals to adjust follow-up management to the needs of women with early stage BC. For instance, our results show that women with early stage BC may benefit from a more multidisciplinary treatment: not only focussing on the medical aspects, but also discussing the psychological, social, and environmental aspects of BC [11]. Our findings have also methodological implications for the use of composite scores in (HR)QOL studies. Composite scores are often obtained by averaging scores across domains. Our study clearly shows that different aspects of life are important at different points in time. This kind of information is lost, when a composite score is used.

Some caution is needed, when interpreting our results. In this study, we only included women with early stage BC (disease stage ≤ 2). Therefore, it is possible that women with more advanced BC will show a different pattern of QOL facets predicting overall QOL across time. In addition, this sample consisted of women only, possibly affecting the results. It is conceivable that in men other aspects, such as financial resources are more important determinants of overall QOL than in women. A major strength of this study is the longitudinal follow-up design. Due to this design, it provides insight into the longitudinal effects of QOL domains and facets on overall QOL [11]. Besides the inclusion of patients in different disease stages, it would be interesting to further extend the follow-up period in future studies. BC patients may experience a number of different stages of survival during their lives and their specific needs at these stages may differ [14].

Information regarding changes in the prediction pattern of overall QOL over time may have important implications for clinical practice. In particular this information may help to provide psychological interventions that have a positive impact on QOL. This study identified variables that play a major role in

predicting overall QOL across time. The outcomes suggest that clinicians and caregivers should focus on different domains and facets of QOL in order to improve QOL of BC patients. To paraphrase George Orwell: all domains and all facets are important, but some of them are more important than others. Some of the time!

In conclusion, our results indicate that in early stage BC positive feelings and personal relationships are the predominant contributors to overall QOL during the first year after surgical treatment.

References

1. Netherlands Cancer Registry. Most prevalent cancer types [Meest voorkomende kankersoorten]. In: http://www.ikcnet.nl/page.php?id=1868&nav_id=114; 2005.
2. SignaleringscommissieKanker. Cancer in the Netherlands. Trends, prognosis, and implications for care demands [Kanker in Nederland. Trends, prognoses en implicaties voor zorgvraag]. KWF Kankerbestrijding; 2004.
3. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233-1241.
4. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227-1232.
5. Van der Steeg AF, De Vries J, Roukema JA. Quality of life and health status in breast carcinoma. Eur J Surg Oncol 2004;30:1051-7.
6. Cella D, Tulsky DS. Measuring quality of life today: Methodological aspects. Oncology 1990;5:29-38.
7. Orley J, Saxena S, Herrman H. Quality of life and mental illness. Reflections from the perspective of the WHOQOL (editorial). Br J Psychiatry 1998;172:291-293.
8. WHOQOL group. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med 1995;41:1403-1409.
9. Spilker B. Introduction to the field of Quality of Life trials. In: Spilker, B (Ed.). Quality of Life Assessments in Clinical Trials. New York: Raven Press; 1990.
10. Dagnelie PC, Pijls-Johannesma MC, Lambin P, Beijer S, De Ruysscher D, Kempen GI. Impact of fatigue on overall quality of life in lung and breast cancer patients selected for high-dose radiotherapy. Ann Oncol 2007;18:940-944.

11. Arnold R, Ranchor AV, Sanderman R, Kempen GI, Ormel J, Suurmeijer TP. The relative contribution of domains of quality of life to overall quality of life for different chronic diseases. Qual Life Res 2004;13:883-896.
12. Beijer S, Kempen GI, Pijls-Johannesma MC, de Graeff A, Dagnelie PC. Determinants of overall quality of life in preterminal cancer patients. Int J Cancer 2008;123:232-235.
13. Leventhal H, Colman S. Quality of life: a process view. Psychology and health 1997;12:753-767.
14. Lu W, Cui Y, Chen X, Zheng Y, Gu K, Cai H, et al. Changes in quality of life among breast cancer patients three years post-diagnosis. Breast Cancer Res Treat 2009;114:357-369.
15. WHOQOL Group. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc Sci Med 1998;46:1569-1585.
16. De Vries J, Van Heck GL. The World Health Organization Quality of Life assessment instrument (WHOQOL-100): validation study with the Dutch version. Eur J Psychol Assess 1997;13:164-178.
17. Power M, Harper A, Bullinger M. The World Health Organization WHOQOL-100: tests of the universality of Quality of Life in 15 different cultural groups worldwide. Health Psychol 1999;18:495-505.
18. WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol Med 1998;28:551-558.
19. Den Oudsten BL, Van Heck GL, Van der Steeg AF, Roukema JA, De Vries J. The WHOQOL-100 has good psychometric properties in breast cancer patients. J Clin Epidemiol 2009;62:195-205.
20. O'Carroll RE, Smith K, Couston M, Cossar JA, Hayes PC. A comparison of the WHOQOL-100 and the WHOQOL-BREF in detecting change in quality of life following liver transplantation. Qual Life Res 2000;9:121-124.
21. Andritsch E, Dietmaier G, Hofmann G, Zloklikovits S, Samonigg H. Global quality of life and its potential predictors in breast cancer patients: an exploratory study. Support Care Cancer 2007;15:21-30.

Chapter 4
Predictors of depressive symptoms 12 months after surgical treatment of early stage breast cancer*

* Den Oudsten BL, Van Heck GL, Van der Steeg AFW, Roukema JA, De Vries J. Predictors of depressive symptoms 12 months after surgical treatment of early stage breast cancer. Psycho-oncology (in press).

Abstract

Objective: Nearly half of the women with breast cancer (BC) show depressive symptoms in the first year after diagnosis. This has a major impact on patients' lives. Therefore, the aim of this study was to identify predictors of depressive symptoms 12 months after surgical treatment. Furthermore, the stability of depressive symptoms across 12 months was investigated for persons scoring high versus low/moderately on agreeableness, trait anxiety, and neuroticism. *Methods*: From the 609 women with an abnormality in the breast, 223 appeared to have early stage BC. A depressive symptoms questionnaire (CES-D) was completed before diagnosis and 1, 3, 6, and 12 months after surgical treatment. In addition, patients completed questionnaires on personality (STAI, NEO-FFI), fatigue (FAS), and aspects of quality of life (WHOQOL-100). *Results:* Before diagnosis and one year later, 40.9% and 27.8% of the women, respectively, scored above the established cut-off score for depressive symptoms. Depressive symptoms significantly improved in this period. Patients reported higher scores, when they had a breast conserving therapy (BCT), scored low on agreeableness, scored high on neuroticism, or reported higher scores on depressive symptoms or fatigue before diagnosis. Other clinical and sociodemographic factors did not predict depressive symptoms. *Conclusions*: Besides BCT, fatigue, and depressive symptoms, personality, especially neuroticism and agreeableness, predicted depressive symptoms one-year after surgical treatment. Therefore, it is important to screen patients on these characteristics in order to prevent long-term depressive symptoms.

Introduction

Breast cancer (BC) is the most common type of malignancy among women in Europe. BC was responsible for 17.6% of all deaths in 2006 [1]. In the Netherlands, one in every nine women will develop carcinoma in situ or invasive carcinoma of the breast during her life [2]. Nowadays, a lot of women survive BC due to early detection of cancer by screening programmes [3].

BC patients have a high risk of developing mood disorders. There is a growing body of studies demonstrating this. Studies examining clinically significant depression, however, show a wide array of estimated depression rates due to differences in study population (e.g., disease stage, treatment stage), study design (e.g., the criteria used to define depression) and choice of measures [4, 5]. In spite of these discrepancies the overall picture is that during the first year following a BC diagnosis, nearly 50% of the women with early stage BC scored high on depression and/or anxiety [6]. Compared with the general female population, the prevalence of depression in women with early stage BC is twice as high [6].

Depression has a detrimental impact on patients' lives [7-9], adversely affects compliance with medical treatment [10], significantly influences recovery from treatment [11], and may reduce survival length [12-14]. In addition, women with depression experience more side-effects of treatment [15]. Major depression and depressive symptoms are frequently underrecognized and undertreated among breast cancer patients [4, 16]. Therefore, the identification of predictive factors for depressive symptoms in patients is important. In this way, screening tools including items assessing these predictive factors can be developed. Then, the detection of women at risk of developing symptoms can be improved in early stage and consequently more adequate support can be provided.

Various risk factors fitting the biopsychosocial model have been examined in the literature. However, previous studies differ substantially with respect to their study design, sample size, concepts assessed, and populations examined, as well as factors under consideration. Due to these discrepancies, there are striking inconsistencies regarding the role of clinical factors and their association with clinical depression (i.e., DSM-IV) or depressive symptoms (i.e., self-report). Some studies have shown that clinical factors, such as type of

surgery, disease stage or adjuvant therapy, were not associated with depressive symptoms [17, 18]. Other studies, in contrast, found that higher levels of depressive symptoms were predicted by axillary lymph node involvement [5] or the presence of pain [18].

With regard to socio-demographics, younger age was negatively associated with depressive symptoms [6, 18, 19]. The lack of a confiding intimate relationship appeared to be a determinant for clinical depression and anxiety at 4 to 12 months after diagnosis [6]. Furthermore, perceived adequacy and network characteristics were significantly associated with less depression [18, 20, 21], however, only in young female patients [18, 21]. Greater risk for depressive symptoms was associated with more stressful life events, less optimism, ambivalence concerning the expression of negative emotions, sleep disturbance, and poorer social functioning [17]. Some studies have examined the role of personality factors with regard to psychological distress in BC. For instance, trait anxiety predicted psychological distress in BC patients on average 21 months after surgery [18]. Women with psychological distress were, in general, characterized by an increased level of anxiety, intrusive thoughts, serious health complaints, and sleeping problems. Pessimists, compared with optimists, had a three times greater risk of experiencing depressive symptoms one year after BC surgery [22]. Recently, it was found that neuroticism may increase the risk for developing depressive symptoms in women with BC [23].

In sum, the existing literature shows that socio-demographic, clinical, and personality factors predict depressive symptoms in breast cancer. Although, a wide range of predictors of depressive symptoms has been found, until now each study has focussed on rather limited sets of predictors. Consequently, there is a need for studies examining a broad range of factors reflecting socio-demographic, clinical, social as well as psychological variables, including personality traits. Given the scarcity of studies and the many inconsistencies in the outcomes of these studies, the current study is rather exploratory.

Thus, the aim of this prospective follow-up study was to explore these factors in depressive symptoms one year after surgical treatment. Furthermore, the stability of depressive symptoms across 12 months was investigated in relation to personality. Concerning personality, we hypothesized that, in addition to clinical predictors like adjuvant therapy and type of surgery, trait anxiety and

neuroticism would predict depressive symptoms 12 months after surgery. In addition, we hypothesized that perceived social support would be associated with depressive symptoms.

Method

Participants

Women with a palpable lump in the breast or an abnormality on a screening mammography were referred by their general practitioner to the Department of Surgery of the outpatient clinics of the St. Elisabeth Hospital (Tilburg, The Netherlands), the Maasland Hospital (Sittard, The Netherlands), or the Jeroen Bosch Hospital (Den Bosch, The Netherlands). The present study is part of a large research program focusing on the role of personality in quality of life of BC patients who had a choice between breast conserving therapy (BCT; i.e. removal of the tumor by means of a lumpectomy and axillary lymph node dissection followed by radiation of the breast) or mastectomy (MTC; i.e. removal of all breast tissue including the nipple). The data were collected from September 2002 until September 2006. From the 799 eligible women, 609 (76.2%) completed the first set of questionnaires before they visited the surgeon or radiologist, i.e. before the diagnosis, benign or malignant, was known (Time-1). In this group (N = 609), 223 appeared to have early stage BC of whom 144 women (63.7%) also completed the depressive symptoms questionnaire one year after surgical treatment (Time-5). The main reasons for not participating were the length of the questionnaires and the amount of experienced stress. Women who had a history of abnormalities in the breast, either benign or malignant, or were suspected of having a breast tumor that was too large (>5 centimeter) to allow a choice between both types of surgery, were not included in the study. In order to participate, the women had to be able to read Dutch. After the baseline measurement (Time-1; N = 223), women completed questionnaires at 1 (Time-2; N = 178), 3 (Time-3; N = 171), 6 (Time-4; N = 167), and 12 (Time-5; N = 164) months after surgical treatment. Participation in the study was not known to the treating surgeon. The local ethics committee approved the study. All participants gave written informed consent.

Measures

Questionnaires assessing socio-demographic factors (marital status, children, paid work, and education level), psychological factors (depressive symptoms, fatigue, sleep and rest, self-esteem, body image, subjective cognitive functioning, pain and discomfort, social support), and personality were completed at Time-1. At the other time points women again completed a depressive symptoms questionnaire.

Basic personality factors were assessed with the Neuroticism-Extraversion-Openness-Five Factor Inventory (NEO-FFI) [24, 25, 26] and the State Trait Anxiety Inventory [27, 28]. The NEO-FFI is a self-report questionnaire consisting of 60 statements covering five broad dimensions of personality: neuroticism (i.e., the tendency to experience distressing emotions, such as fear, guilt, and frustration), extraversion (i.e., the disposition towards cheerfulness, sociability, and high activity), openness to new experiences (i.e., the tendency to have a receptive orientation towards varied experiences and ideas), agreeableness (i.e., the inclination towards interpersonal trust and consideration of others), and conscientiousness (i.e., the tendency towards persistence, sense of duty, organizing, planning, and self-discipline). Each statement is rated on a 5-point scale ranging from 1 (*strongly disagree*) to 5 (*strongly agree*), resulting in dimension scores between 12 and 60. The internal consistency, test-retest reliability, as well as the convergent validity, are acceptable to good [26].

The STAI consists of two 20-item scales for measuring state anxiety and trait anxiety. In the present study, only the Trait Anxiety scale was used, which describes how persons generally feel and conceives of anxiety as a personality disposition. The STAI trait scale has a 4-point rating scale (1 (*almost never*) to 4 (*almost always*)). The Dutch version of the STAI-Trait scale has good reliability and validity [28].

The Center for Epidemiological Studies- Depression Scale (CES-D) [29] is a 20-item self-report scale measuring the presence and degree of depressive symptoms over the past week. The rating scale ranges from 0 (*seldom or never)* to 3 (*(almost) always*). Scores can range from 0 to 60. The CES-D has been established as a valid and reliable measure of depressive symptoms in BC patients 30. Reliability and criterion validity are good [31, 32].

The Fatigue Assessment Scale (FAS) [33] is a 10-item questionnaire assessing perceived fatigue and exhaustion. The response scale is a 5-point rating

scale (1 (*never*) to 5 (*always*)). Scores on the FAS range from 10 to 50. The psychometric properties are good [34-36].

The World Health Organization Quality of Life assessment instrument-100 (WHOQOL-100) [37, 38], is a cross-culturally developed generic multi-dimensional quality of life (QOL) measure. This instrument covers 24 specific facets of QOL, assessed by 96 questions, and one General Health and Overall Quality of Life facet. Each facet is measured with four items using 5-point Likert scales. High facet scores indicate good QOL; except for the facets Pain and Discomfort, Negative Feelings, and Dependence on Medication or Treatments, which are negatively framed. In the present study, six facets (Pain and Discomfort, Cognitive Functions, Sleep and Rest, Self-esteem, Body Image, and Social Support) were used. Reliability and validity [38-40] are adequate and sensitivity [41] is high.

Medical records

Data concerning type of surgery (BCT or MTC), disease stage, tumor size after pathological examination (mm), and adjuvant treatment (chemotherapy, radiotherapy, hormone therapy) were obtained from the medical records of the patients.

Statistical analysis

Frequencies were used to present the available sociodemographic and clinical data. Student t-tests and chi-square tests were used to examine differences between participants and non-participants. As a first step, aiming at minimizing the number of independent variables in the final regression analysis, linear regression analyses (method: stepwise) were performed separately with socio-demographic factors (i.e., age, partner, children, educational level, paid job), clinical factors (i.e., chemotherapy, hormone therapy, radiotherapy, tumor size, disease stage, type of surgery), symptoms (fatigue, pain and discomfort, subjective cognitive functions, sleep and rest), psychological factors (i.e., depressive symptoms (Time-1), self-esteem, body image), personality factors (trait anxiety, neuroticism, extraversion, openness to new experiences, agreeableness, conscientiousness) and social support, as independent variables and depressive symptoms at 12 months as the outcome measure. Subsequently,

the significant predictors of depressive symptoms at 12 months were entered in the final regression analyses (method: stepwise).

General linear model analyses for repeated measures were used to investigate the course of depressive symptoms over the various assessment points. In addition, stability was examined with respect to those factors that proved to be most prominent in the present study: type of surgery, agreeableness and neuroticism. For this purpose, we divided the total scores of agreeableness and neuroticism into two groups. The first group consisted of the stanines ≤5; the second group of stanines ≥6. Partial eta squared (effect size) was derived from the general linear model. An effect size between 0.01 and 0.06 is considered as a small effect by Cohen's definition, while effect sizes between 0.06 and 0.13 and greater than 0.14 are considered as moderate and strong effect sizes, respectively [42]. Multiple post hoc comparisons were corrected with Bonferroni's method. Analyses were performed with SPSS (version 14.0).

Results

Sociodemographic and clinical characteristics of the participants are shown in Table 1. Participants were significantly younger compared with non-participants (p =.002). They did not differ on other sociodemographic or clinical characteristics.

Table 1. Sociodemographic and clinical characteristics of the participants at baseline

	BC group (n=223)
Sociodemographic variables	
Age at diagnosis (mean ± SD)	58.7 (9.4)
Living with a partner (yes/no/missing)	179 (80.3) / 37 (16.6) / 3 (1.3)
Having children (yes/no/missing	191 (85.7) / 29 (13.0) / 3 (1.3)
Educational level	
0-9 yrs/10-14 yrs/> 14 yrs/missing)	85 (38.1) / 95 (42.6) / 37 (16.6) 2 (0.9)
Paid work (yes/no/missing)	85 (38.1) / 135 (60.5) / 1 (0.4)
Diameter of tumor	
< 1cm / 1-3 cm / > 3 cm	49 (22.0) / 146 (65.5) /25 (11.2)
Type of surgery	
BCT/MTC/no surgical treatment	107 (48.0) / 114 (51.1) / 2 (0.9)
Adjuvant therapy (yes/no)	169 (75.8) / 54 (24.2)
Disease stage	
Stage 0	24 (10.8)
Stage I	93 (41.7)
Stage IIa	69 (30.9)
Stage IIb	35 (15.7)
Indefinable	2 (0.9)

Note: For the sociodemographics, percentages are between brackets (except for age).
Abbreviations: MTC = modified radical mastectomy; BCT = breast conserving therapy

None of the sociodemographic factors predicted depressive symptoms scores at Time-5. The only clinical factor that predicted depressive symptoms at Time-5 was type of surgery (β= -.205, p= .017). Fatigue (β= .492, p<.0001) and sleep and rest (β= -.162, p= .032), and depressive symptoms (β= .354, p< .0001) at Time-1 contributed significantly to the prediction of depressive symptoms at Time-5. In addition, social support (β= -.223, p= .008) also predicted depressive symptoms. Furthermore, neuroticism (β= .218, p= .020), agreeableness (β= -.155, p= .047), and trait anxiety (β= -.155, p < .0001) predicted depressive symptoms at Time-5 (see Table 2). In the final analysis, depressive symptoms at Time-5 was predicted by type of surgery, depressive symptoms at Time-1, fatigue at Time-1, neuroticism, and agreeableness, explaining 39.8% of the variance (F = 18.71, p < .0001; see Table 3).

Table 2. Regression analyses (stepwise) for depressive symptoms (Time-5) in women with early stage BC

Predictors	Beta	p-value	Adjusted R^2 (F-value, p-value)
Age at baseline		ns	
Children (yes/no)		ns	
Partner (yes/no)		ns	
Paid work (yes/no)		ns	
Educational level		ns	
Disease stage		ns	
Chemotherapy		ns	
Hormone therapy		ns	
Radiotherapy		ns	
Tumor size		ns	.035
Type of surgery	-.205	.017	(F = 5.880, p = .017)
Fatigue (Time-1)	.492	<.0001	
Pain and discomfort (Time-1)		ns	
Cognitive functions (Time-1)		ns	.306
Sleep and rest (Time-1)		.032	(F = 31.434, p <.0001)
Depressive symptoms (Time-1)	.519	<.0001	
Self-esteem (Time-1)		ns	.264
Body image (Time-1)		ns	(F = 51.501, p <.0009)
Social support (Time-1)	-.223	.008	.043 (F = 7.186, p = .008)
Neuroticism	.218	.020	
Extraversion		ns	
Openness to experience		ns	
Agreeableness	-.155	.047	
Conscientiousness		ns	.298
Trait anxiety	.331	<.0001	(F = 19.787, p <.0001)

Note. ns = not significant

Table 3. Final regression analysis (stepwise) for depressive symptoms (Time-5) in women with early stage BC

	Beta	p-value	Adjusted R^2 change	Adjusted R^2 (F-value, p-value)
Fatigue (Time-1)	.276	.003	.292	
Neuroticism	.163	.050	.055	
Type of surgery	-.169	.013	.028	
Depressive symptoms	.219	.018	.024	.398
Agreeableness	-.154	.034	.021	(F = 18.710, p <.0001)

Before diagnosis and one year later, 40.9% and 27.8% of the women, respectively, scored above the established cut-off score for depressive symptoms.

Concerning the stability of depressive symptoms across assessment points (Figure 1), an effect for time was found (Wilks' Lambda = .78, $F(4,101) = 7.30$, $p<.0001$, partial eta squared = .224, observed power = .995). Mean scores of depressive symptoms at Time-1 (14.78 ± 9.74) were statistically different from scores at Time-4 (11.45 ± 10.24; p = .002) and the mean scores of depressive symptoms at Time-5 (10.33 ± 8.35) were statistically different from scores at Time-1 (14.78 ± 9.74), Time-2 (12.97 ± 9.77), and Time-3 (12.58 ± 10.15).

With regard to agreeableness, no significant improvements were found in depressive symptoms across time (Figure 2). In addition, no significant interaction effect between time and agreeableness was found.

With regard to neuroticism, a significant improvement in depressive symptoms across time was found (Wilks' Lambda = .80, $F(4,93) = 5.66$, $p<.0001$, partial eta squared = .196, observed power = .975; see Figure 3).

Figure 1. Course of depressive symptoms across 12 months in women with early stage BC

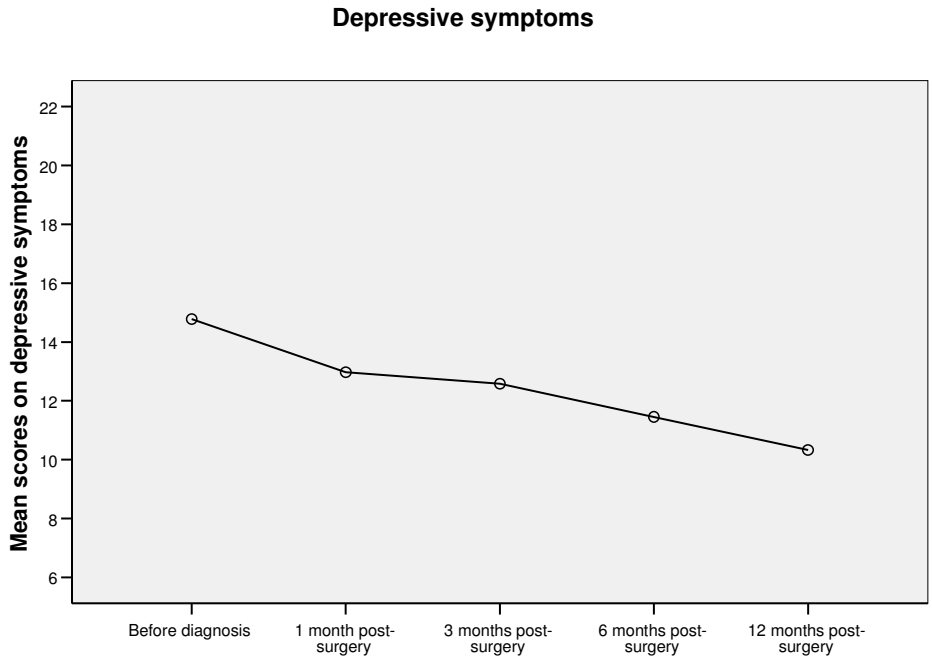


Figure 2. Course of depressive symptoms across 12 months in women with early stage BC scoring high or low/moderate on agreeableness

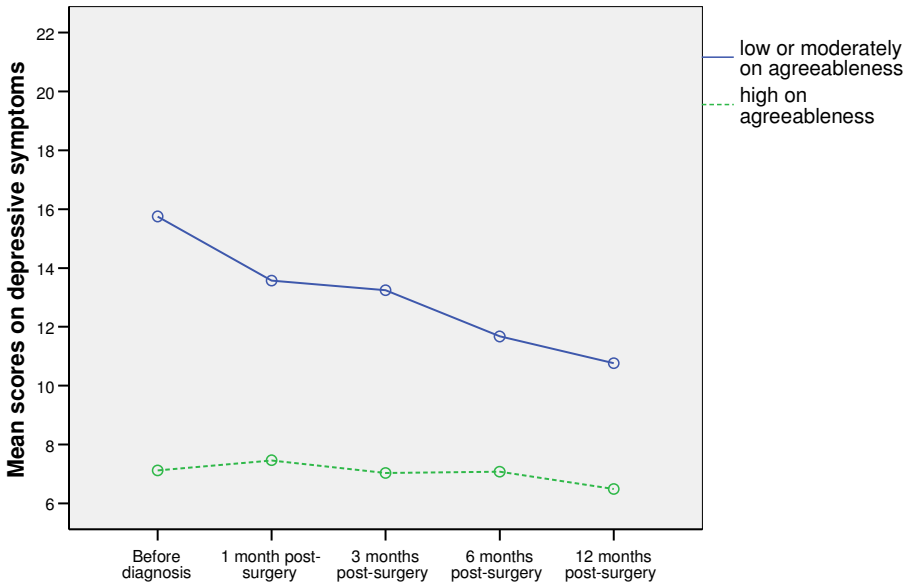


Figure 3. Course of depressive symptoms across 12 months in women with early stage BC scoring high or low/moderate on neuroticism

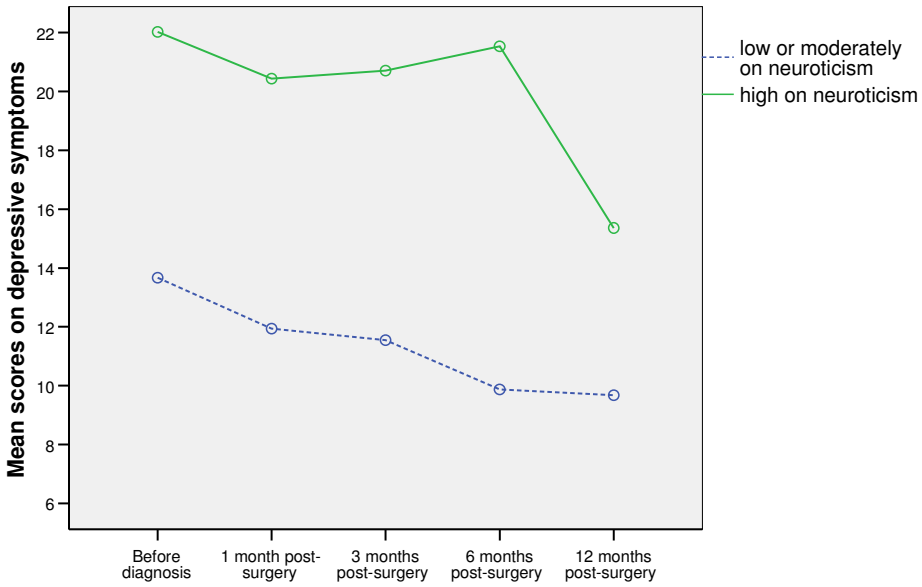
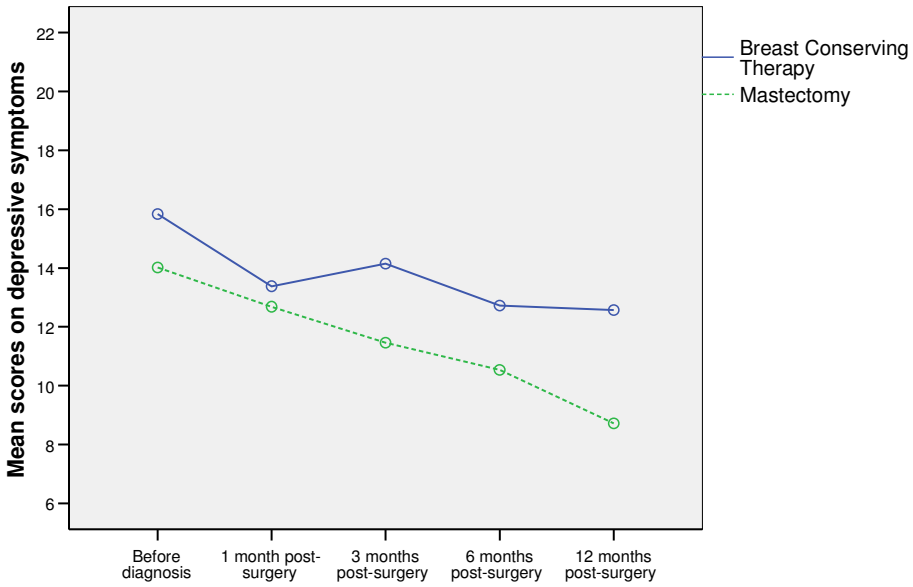


Figure 4. Course of depressive symptoms across 12 months in women with early stage BC with breast conserving therapy or mastectomy



Mean scores of depressive symptoms at Time-5 (10.19 ± 8.22) were statistically different from scores at earlier time points (p<.05). No interaction effects between time and neuroticism were found.

With regard to type of surgery, a significant improvement in depressive symptoms across time was found (Wilks' Lambda = .79, F(4,100) =6.61, p < .0001, partial eta squared = .209, observed power = .990; see Figure 4). Mean scores of depressive symptoms at Time-5 (10.33 ± 8.35) were statistically different from scores at earlier time points (p < .05), except for Time-4. In addition, Time-1 (14.78 ± 9.74) differed significantly from Time-4 (11.45 ± 10.24, p = .002). No interaction effects between time and type of surgery were found.

Discussion

The aim of the present prospective follow-up study was to examine predictors of depressive symptoms 12 months after surgical treatment in women with early stage BC. In addition, we examined the stability of depressive symptoms. As such, this study adds knowledge to describing those patients who are at risk of developing depressive symptoms, so that screening and interventions can be aimed at high-risk patients in order to reduce subsequent morbidity. Depressive symptoms at Time-5 were predicted by lower scores on agreeableness, higher scores on neuroticism, depressive symptoms at Time-1, fatigue at Time-1, or type of surgery. Socio-demographic factors did not play a significant role.

Existing studies are inconclusive regarding the association between clinical variables and depressive symptoms [5, 6, 17, 18], i.e. studies have shown no differences between types of surgery [6, 17, 43] or slightly favored BCT [43, 44]. We found that women with MCT had less chance to experience depressive symptoms one-year after surgical treatment compared to women who had received BCT. This result cannot be easily explained. It should be emphasized that in the present study women had a choice between BCT and MTC. To what extent women feel that they had received the 'wrong' type of surgery is unknown. However, one could argue that a subtype of women would worry about whether the surgeon had removed enough tissue [45]. For instance, women scoring high on trait anxiety and / or neuroticism might perceive BCT as a greater threat than

women scoring low or moderately on these traits. Consistent with the literature [17, 18], women who received adjuvant therapy and were relatively satisfied with their level of social support were not at risk for developing depressive symptoms in our study. Previous identified risk factors, like, self-esteem and bodily pain, were not contributing significantly to the prediction of depressive symptoms in our study [18].

To the best of our knowledge no previous study has longitudinally examined the relationship between several broad personality characteristics and depressive symptoms in early stage BC patients. Following the findings of Golden-Kreutz and Andersen [23], we hypothesized that neuroticism would be positively associated with depressive symptoms at Time-5. We found that in the multivariate analysis agreeableness and neuroticism contributed significantly to the prediction of depressive symptoms. With regard to neuroticism, this finding is consistent with the study of Golden-Kreutz and Andersen [23]. In spite of the fact that, a strong positive association between trait anxiety and depressive symptoms at Time-5 could be demonstrated, trait anxiety did not provide a substantial increment of explained variance on top of neuroticism, presumably due to the overlapping content of both variables. Neuroticism is characterized by a general disposition to experience distressing emotions, such as fear, guilt, and frustration [25]. Costa and McCrae [25] distinguish six aspects of neuroticism: Vulnerability to Stress, Impulsiveness, Self-Consciousness, Depression, Hostility, and Anxiety. Theoretically, neuroticism only shows a minor overlap with trait anxiety [46]. In this study, trait anxiety accounts for 34.3% of the variability in neuroticism. Consequently, trait anxiety can also be defined individually. Trait anxiety refers to the tendency to respond to situations perceived as threatening with a rise in anxiety intensity [27]. Agreeableness represents the inclination towards interpersonal trust and consideration of others. Persons scoring high on agreeableness tend to be warm, sympathetic, cooperative, and are inclined to avoid conflict [25]. However, agreeableness is not frequently assessed in studies on depression [47]. An explanation for our current finding could be that persons who score high on agreeableness tend to have enough social support or perceive the actual social support as adequate. Among patients with kidney disease, Hoth et al. [48] tested the hypothesis that the association between social support and depressive symptoms would vary as a function of individual differences in

agreeableness. In patients high in agreeableness, greater social support was associated with a reduction in depressive symptoms over a period of approximately 18-months. In contrast, for patients low in agreeableness, social support had little effect on depressive symptoms. This effect was observed after controlling for initial level of depression and disease progression during the follow-up period. In the present study, no significant interactions were found, between time and agreeableness showing that agreeableness did not act as a moderator variable [49]. However, agreeableness was a mediator of depressive symptoms (results not shown).

Notwithstanding the fact that personality traits are relatively stable over time, these women still might benefit significantly from adequate forms of psycho-education and consequently might learn to understand how a person's characteristics interfere with labeling and perceiving situations and subsequently affect behavior.

The current study consisted of a rather homogenous group of women with early stage BC (T1 and T2 stage). It might be that women with a more advanced cancer (T3 and T4 stage) would experience a greater threat to survival [18]. Consequently, levels of depressive symptoms may increase or depressive symptoms [18] may be experienced for a longer period of time. In other words, scores of depressive symptoms may be more stable in women with advanced breast cancer. However, women in this study all had early stage BC. The more severe cases of BC were not present in this sample. Therefore, these results should not be generalized to other populations, for instance, women with more severe cancer stages or women with recurrent breast cancer. Studies like the current one often show relatively high attrition [50]. Also our study had only 63.7% of the women with early stage BC still in the study at one-year after surgical treatment. This might have influenced our results. In addition, the sample size in this study was relatively small. Furthermore, some important factors, including co-morbidity, possible psychiatric history, and information whether any of the women had received treatment for mental health problems have not been included. Therefore, results should be interpreted with caution and replication is desirable. Future studies should further examine the relationship between personality characteristics and the presence of depressive symptoms.

In conclusion, agreeableness, depressive symptoms, fatigue (all at Time-1), and type of surgery have a profound effect on experiencing depressive symptoms at Time-5. Since depressive symptoms adversely affect patients' lives [8-12, 15], it is of utmost importance to screen women with early stage BC for the risk factors that we found and subsequently offer them psychological interventions focusing on dealing with stressful situations.

References

1. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007;18:581-592.
2. Association of Comprehensive Cancer Centres. Incidence of cancer in the Netherlands. Utrecht: Drukkerij De Kempen, 1998.
3. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43-66.
4. Fann JR, Thomas-Rich AM, Katon WJ, et al. Major depression after breast cancer: a review of epidemiology and treatment. Gen Hosp Psychiatry 2008;30:112-126.
5. Christensen S, Zachariae R, Jensen AB, et al. Prevalence and risk of depressive symptoms 3-4 months post-surgery in a nationwide cohort study of Danish women treated for early stage breast-cancer. Breast Cancer Res Treat 2009;113:339-355.
6. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. BMJ 2005;330:702.
7. Deshields T, Tibbs T, Fan MY, Taylor M. Differences in patterns of depression after treatment for breast cancer. Psycho-oncology 2006;15:398-406.
8. Visser MR, Smets EM. Fatigue, depression and quality of life in cancer patients: how are they related? Support Care Cancer 1998;6:101-108.
9. Badger TA, Braden CJ, Mishel MH, Longman A. Depression burden, psychological adjustment, and quality of life in women with breast cancer: patterns over time. Res Nurs Health 2004;27:19-28.
10. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000;160:2101-2107.
11. Walker LG, Heys SD, Walker MB, et al. Psychological factors can predict the response to primary chemotherapy in patients with locally advanced breast cancer. Eur J Cancer 1999;35:1783-1788.

12. Hjerl K, Andersen EW, Keiding N, Mouridsen HT, Mortensen PB, Jorgensen T. Depression as a prognostic factor for breast cancer mortality. Psychosomatics 2003;44:24-30.
13. Watson M, Haviland JS, Greer S, Davidson J, Bliss JM. Influence of psychological response on survival in breast cancer: a population-based cohort study. Lancet 1999;354:1331-1336.
14. Weihs KL, Enright TM, Simmens SJ, Reiss D. Negative affectivity, restriction of emotions, and site of metastases predict mortality in recurrent breast cancer. J Psychosom Res 2000;49:59-68.
15. Badger TA, Braden CJ, Mishel MH. Depression burden, self-help interventions, and side effect experience in women receiving treatment to breast cancer. Oncol Nurs Forum 2001;28:567-574.
16. Rabin EG, Heldt E, Hirakata VN, Fleck MP. Quality of life predictors in breast cancer women. Eur J Oncol Nurs 2008;12:53-57.
17. Bardwell WA, Natarajan L, Dimsdale JE, et al. Objective cancer-related variables are not associated with depressive symptoms in women treated for early-stage breast cancer. J Clin Oncol 2006;24:2420-2427.
18. Wong-Kim EC, Bloom JR. Depression experienced by young women newly diagnosed with breast cancer. Psycho-oncology 2005;14:564-573.
19. Ell K, Sanchez K, Vourlekis B, et al. Depression, correlates of depression, and receipt of depression care among low-income women with breast or gynecologic cancer. J Clin Oncol 2005;23:3052-3060.
20. Hann D, Oxman T, Ahles T, Furstenberg C, Stuke T. Social support adequacy and depression in older patients with metastatic cancer. Psycho-oncology 1995;4:213–221.
21. Hann D, Baker F, Denniston M, et al. The influence of social support on depressive symptoms in cancer patients: age and gender differences. J Psychosom Res 2002;52:279-283.
22. Schou I, Ekeberg O, Ruland CM, Sandvik L, Karesen R. Pessimism as a predictor of emotional morbidity one year following breast cancer surgery. Psycho-oncology 2004;13:309-320.
23. Golden-Kreutz DM, Andersen BL. Depressive symptoms after breast cancer surgery: relationships with global, cancer-related, and life event stress. Psycho-oncology 2004;13:211-220.

24. Costa PT, McCrae RR. The NEO Personality Inventory Manual. Odessa, FL: Psychological Assessment Resources Inc., 1985.
25. Costa PT, McCrae RR. Revised NEO Personality Inventory (NEO-PI-R) and NEO Five Factor Inventory (NEO-FFI) professional manual. Odessa, FL: Psychological Assessment Resources Inc., 1992.
26. Hoekstra H, Ormel J, De Fruyt F. Handleiding NEO persoonlijkheidsvragenlijsten NEO-PI-R en NEO-FFI [manual NEO personality questionnaires NEO-PI-R and NEO-FFI]. Lisse, The Netherlands: Swets Test Services, 1996.
27. Spielberger CD, Gorsuch RL, Lushene RE. STAI manual for the State-Trait Anxiety Inventory. Palo-Alto, CA: Consulting Psychologists Press, 1970.
28. Van der Ploeg HM, Defares PB, Spielberger CD. ZBV: a Dutch-language adaptation of the Spielberger State-Trait Anxiety Inventory. Lisse, The Netherlands: Swets & Zeitlinger, 1980.
29. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385-401.
30. Hann D, Winter K, Jacobsen P. Measurement of depressive symptoms in cancer patients: evaluation of the Center for Epidemiological Studies Depression Scale (CES-D). J Psychosom Res 1999;46:437-443.
31. De Rijk AE, Schreurs KMG, Bensing JM. What is behind "i'm so tired"? fatigue experiences and their relations to the quality and quantity of external stimulation. J Psychosom Res 1999;47:509-523.
32. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. Psychol Med 1997;27:231-235.
33. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: the Fatigue Assessment Scale. J Psychosom Res 2003;54:345-352.
34. De Vries J, Michielsen H, Van Heck GL, Drent M. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). Br J Health Psychol 2004;9:279-291.

35. Michielsen HJ, De Vries J, Drent M, Peros-Golubicic T. Psychometric qualities of the Fatigue Assessment Scale in Croatian sarcoidosis patients. Sarcoidosis Vasc Diffuse Lung Dis 2005;22:133-138.
36. Michielsen H, De Vries J, van Heck GL, Van de Vijver A, Sijtsma K. Examination of the dimensionality of fatigue: the construction of the Fatigue Assessment Scale (FAS). Eur J Psychol Assess 2004;20:39-48.
37. WHOQOL Group. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc Sci Med 1998;46:1569-1585.
38. De Vries J, Van Heck GL. The World Health Organization Quality of Life assessment instrument (WHOQOL-100): validation study with the Dutch version. Eur J Psychol Assess 1997;13:164-178.
39. Power M, Harper A, Bullinger M. The World Health Organization WHOQOL-100: tests of the universality of Quality of Life in 15 different cultural groups worldwide. Health Psychol 1999;18:495-505.
40. Den Oudsten BL, Van Heck GL, Van der Steeg AF, Roukema JA, De Vries J. The WHOQOL-100 has good psychometric properties in breast cancer patients. J Clin Epidemiol 2009; 62:195-05.
41. O'Carroll RE, Smith K, Couston M, Cossar JA, Hayes PC. A comparison of the WHOQOL-100 and the WHOQOL-BREF in detecting change in quality of life following liver transplantation. Qual Life Res 2000;9:121-124.
42. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum, 1988.
43. Fallowfield LJ. Psychosocial adjustment after treatment for early breast cancer. Oncology (Williston Park) 1990;4:89-97; discussion 97-88, 100.
44. Holmberg L, Omne-Ponten M, Burns T, Adami HO, Bergstrom R. Psychosocial adjustment after mastectomy and breast-conserving treatment. Cancer 1989;64:969-974.
45. Fallowfield LJ, Baum M, Maguire GP. Effects of breast conservation on psychological morbidity associated with diagnosis and treatment of early breast cancer. Br Med J (Clin Res Ed) 1986;293:1331-1334.

46. Eysenck MW. Cognitive approaches to trait anxiety. In: Eliasz A, Hampson SE, De Raad B, eds. Advances in personality psychology: Psychology Press, 2005:1-18.
47. Bagby RM, Rector NA. Self-criticism, dependency and the five factor model of personality in depression: assessing construct overlap. Person Individ Dif 1998;24:895-897.
48. Hoth KF, Christensen AJ, Ehlers SL, Raichle KA, Lawton WJ. A longitudinal examination of social support, agreeableness and depressive symptoms in chronic kidney disease. J Behav Med 2007;30:69-76.
49. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51:1173-1182.
50. Arving C, Glimelius B, Brandberg Y. Four weeks of daily assessments of anxiety, depression and activity compared to a point assessment with the Hospital Anxiety and Depression Scale. Qual Life Res 2008;17:95-104.

Chapter 5
Second operation is not related to psychological outcome in breast cancer patients*

* Den Oudsten BL, Van Heck GL, Van der Steeg AFW, Roukema JA, De Vries J. Second operation is not related to psychological outcome in breast cancer patients (Submitted for publication).

Abstract

Objective: To examine the effect of multiple surgical treatments on psychological outcomes in women with early stage breast cancer (BC). *Methods:* Questionnaires for depressive symptoms (CES-D), fatigue (FAS), anxiety (STAI-State), physical health (WHOQOL-100), psychological health (WHOQOL-100), and overall quality of life and general health (WHOQOL-100) were completed before diagnosis (Time-1) and 1 (Time-2), 3 (Time-3), 6 (Time-4), and 12 (Time-5) months after the last surgical treatment. *Results:* From the 217 participating women with early stage BC, 78 (35.9%) needed an additional surgical treatment. Eight persons (10.4%) received a second operation due to complications. Twenty-two women (28.6%) were converted from BCT to MTC in a second surgery. After adjusting for type of surgery, disease stage, and hormonal therapy, psychological outcomes did not significantly change over time, with the exception of anxiety [Wilks' Lambda = .72, $F(4,86) = 8.55$, $p<.0001$, partial eta squared = .29, observed power = 1.00]. On average, women with one and women with two surgical treatments did not differ on any outcome measure. No interaction effects were found, indicating that changes in outcomes over time were the same for both groups. *Conclusions:* Women who had a repeat surgical treatment did not score differently on psychological outcome measures compared with women who were treated 'efficiently'.

Introduction

Breast cancer (BC) is the most common malignancy in women [1] and the most frequent cause of death in women aged 35 to 60 years in Europe [2]. In the Netherlands, one in every nine women will develop breast cancer before the age of 85 [3]. The prevalence of BC increases with age from 3-4% at age 50-69 to 6% of women older than 70 [4].

Surgical treatment is usually the initial treatment for invasive early stage BC. Surgical options include breast conserving therapy (i.e., lumpectomy and a sentinel node procedure or axillary lymph node dissection followed by radiotherapy; BCT) or mastectomy (i.e., removal of the breast and sentinel node procedure or axillary lymph node dissection; MTC). Although physicians strive to treat women as effectively as possible, i.e. with a minimum of surgical treatments, in practice this is not always possible. For instance, some of the women with early stage BC who initially received BCT appear to need additional surgery when the margin of tissue around the tumor is not cancer-free. It is estimated that of patients undergoing BCT 30 to 60% will require a re-excision for residual tissue [5]. The majority of studies examining the effects of surgical treatment in oncology have focused on the effects of type of surgery or adjuvant therapy on clinical [6, 7] or psychosocial outcomes [8-14]. Recently, several studies have focused on determining those clinical factors which may be associated with re-excision after BCT [5, 15-18]. To the best of our knowledge, it remains unclear whether there is a relationship between the number of surgical treatments women receive after BC diagnosis and psychological outcomes. Therefore, the aim of this prospective follow-up study was to examine the relationship between second surgery and psychological outcomes (i.e., state anxiety, fatigue, depressive symptoms, and aspects of quality of life). We hypothesize that both groups will improve over time with regard to the selected psychological outcomes, but that women with re-excisions will temporarily have more negative scores. We also expect that differences between the groups will not be significant at 12-months after surgical treatment.

Method

Women with a palpable lump in the breast or an abnormality on a screening mammography were referred by their general practitioner to the Department of Surgery of the outpatient clinics of the St. Elisabeth Hospital (Tilburg), the Maasland Hospital (Sittard), or the Jeroen Bosch Hospital (Den Bosch) in The Netherlands. The present study is part of a larger study that focuses on the role of personality on the quality of life in women with early stage BC who could choose between breast conserving and ablative surgical treatment. The inclusion of patients took place from September 2002 until September 2006. From the 799 eligible women, 609 (76.2%) completed the first set of questionnaires before they visited the surgeon or radiologist, i.e. before the diagnosis, benign or malignant, was known (Time-1). In this group (N = 609), 225 appeared to have early stage BC; the others had a benign breast problem (BBP).

The main reasons for not participating were the length of questionnaires and the amount of stress at the first visit to the hospital. Women with a history of abnormalities in the breast, benign or malignant, or a breast tumor that was too large (>5 centimeter) for BCT, were excluded from the study. Participants had to be able to read and write in Dutch.

After the baseline measurement before diagnosis (Time-1), the participants were divided in two groups: women with early stage breast cancer (BC group) and women with benign breast problems (BBP group). Thereafter, women completed questionnaires at 1, (Time-2), 3 (Time-3), 6 (Time-4), and 12 (Time-5) months after the last surgical treatment (BC). Only the women with a BC diagnosis participated in the present study. The time points were chosen in such a way that the follow-up measures would not interfere with the time of the treatment modalities. Questionnaires were filled in at home and returned in a stamped addressed envelope. Participation in the study was not known to the surgeon in attendance and, therefore, could not affect treatment and clinical follow-up. All the participants gave written informed consent.

Measures

Questionnaires assessing socio-demographic factors (marital status, children, paid work, and education level) and psychological factors (depressive symptoms,

fatigue, state anxiety, quality of life) were completed at Time-1. At the other time points women again completed questionnaires on psychological factors.

The Center for Epidemiological Studies- Depression Scale (CES-D) [19] is a 20-item self-report scale measuring the presence and degree of depressive symptoms over the past week. The rating scale ranges from 0 (*seldom or never)* to 3 (*(almost) always*). Scores can range from 0 to 60. The CES-D has been established as a valid and reliable measure of depressive symptoms in BC patients [20]. Reliability and criterion validity are good [21, 22].

The Fatigue Assessment Scale (FAS) [23] is a 10-item questionnaire assessing perceived fatigue and exhaustion. The response scale is a 5-point rating scale ranging from 1 (*never*) to 5 (*always*). Scores on the FAS range from 10 to 50. The psychometric properties are good [24-26].

The STAI consists of two 20-item scales for measuring state anxiety and trait anxiety. In the present study, only the State Anxiety scale was used. This scale assesses how persons feel at a particular moment in time. The STAI State scale has a 4-point rating scale ranging from 1 (*almost never*) to 4 (*almost always*). The Dutch version of the STAI-State scale has good reliability and validity [27].

The World Health Organization Quality of Life assessment instrument-100 (WHOQOL-100) [28, Dutch version 29], is a cross-culturally developed generic multi-dimensional quality of life (QOL) measure. This instrument covers 24 specific facets of QOL, assessed by 96 questions, and one General Health and Overall Quality of Life facet. In the present study, only the Overall Quality of Life and General Health facet, the Physical Health domain, and the Psychological Health domain were used. A high facet score indicates good QOL. Reliability and validity [29-31] are adequate and sensitivity [32] is high.

Statistical procedure

Student *t*-tests and Chi-square tests were used to examine the potential differences between participants and non-participants. To examine the influence across time of the number of surgical treatments on depressive symptoms, state anxiety, overall quality of life and general health, physical health, and psychological health, multivariate analysis of variance (MANOVA) with repeated measures were used. Partial eta squared (effect size) was derived from the general linear

model. An effect size between 0.01 and 0.06 is considered as a small effect, while effect sizes between 0.06 and 0.13 and greater than 0.14 are considered as moderate and strong effect sizes, respectively [33]. Multiple post hoc comparisons were corrected with the Bonferroni method. Subsequently, multivariate analysis of covariance (MANCOVA) with repeated measures was used, in which type of surgery (*BCT/MTC*), disease stage, and hormone therapy (*yes/no*) were used as covariates as women with one and two surgical treatments differed on these patient characteristics (see Table 1). A p-value < .05 was considered to be statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Chicago, IL, USA; version 14.0).

Results

At baseline, 225 women completed psychological outcome questionnaires. Figure 1 presents a flow chart of this study. Participants did not differ from non-participants with regard to sociodemographic (i.e., age, partner status, job status, educational level) and clinical (i.e., chemotherapy, radiotherapy, hormone therapy) variables. Eight persons were removed from the analyses, because they did not have surgery (n = 4) or had more than two surgical treatments (n = 4). From the 217 participating women, 79 (36.4%) needed one repeat surgical treatment. Eight persons (10.4%) received a second operation due to complications. Twenty-two women (28.6%) were converted from BCT to MTC in a second surgery. No differences were found between the women who received one or two surgical treatments with regard to sociodemographic variables. However, women differed on the clinical characteristics: hormone therapy (*yes/no*), type of surgery (*BCT/MTC*), and disease stage *(stage 0 / I / IIa / IIb)* (see Table 1).

Concerning fatigue, women with one or two surgical treatments did not score differently on symptoms of fatigue [$F(1,105)=.01$, p = .92]. However, an effect for time was found (See Table 2). Mean scores of fatigue scores at Time-1 (20.03 ± 7.36) were statistically lower than scores at Time-2 (22.95 ± 7.52, $p<.0001$) and Time-3 (22.94 ± 8.09, $p<.0001$). In addition, mean fatigue scores at Time-5 (20.57 ± 7.11) were significantly lower than mean scores at Time-2

(p=.001) and Time-3 (p<.0001). No relationship was found between time and number of surgical treatments. After controlling for clinical factors, the effect for time did not remain significant [Wilks' Lambda = .97, F(4,99) = .89, p=.474, partial eta squared = .04, observed power = .27].

Figure 1. Flow chart of the participants

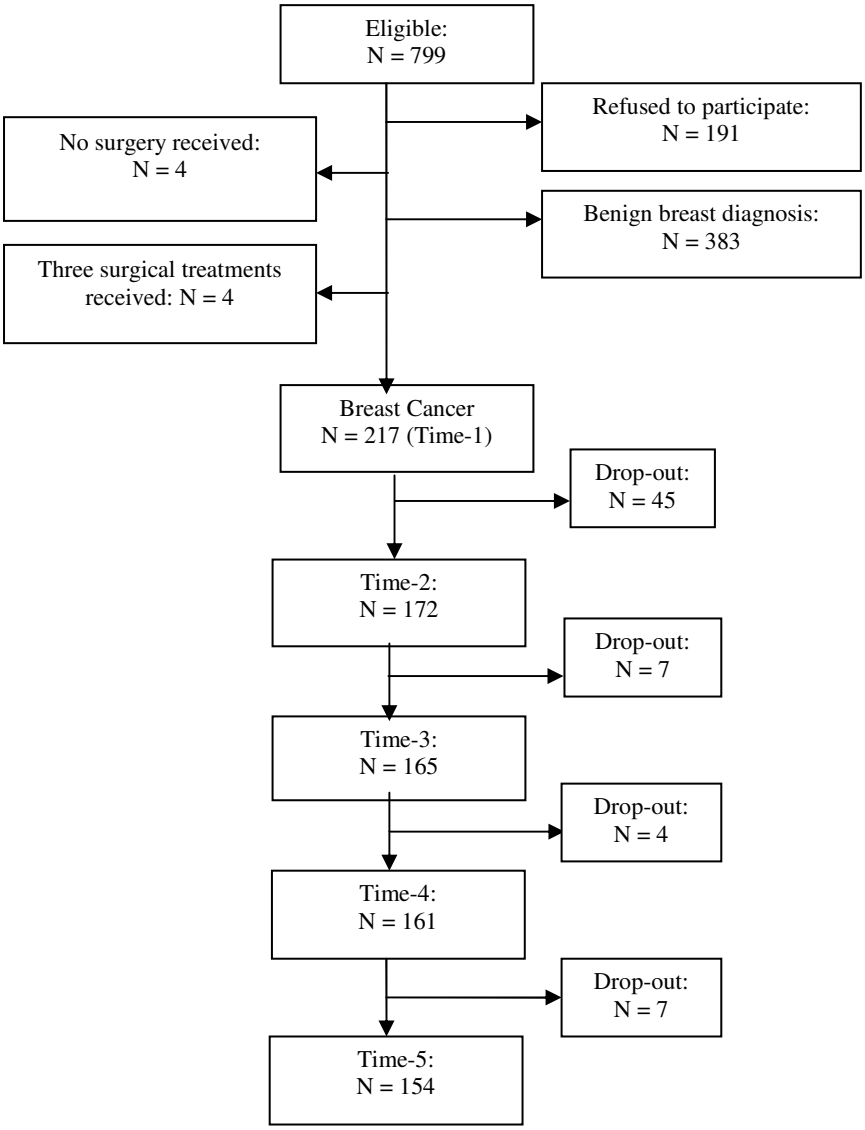


Table 1. Patient characteristics

	Number of operations		
	One (N = 138)	Two (N = 79)	p-value
Sociodemographic			
Age, years (mean ± SD)	59.3 ± 9.1	57.8 ± 9.5	ns
Living with a partner (yes/no/missing)	111 (80.4)/ 24 (17.4)/ 3 (2.2)	65 (82.3)/ 11 (13.9)/ 3 (3.8)	ns
Having children (yes/no/missing)	118 (85.5)/ 19 (13.0)/ 2 (1.4)	66 (83.5)/ 10 (12.7)/ 3 (3.8)	ns
Educational level (0-9/10-14/>14 yrs/missing)	53 (38.4)/ 58 (42.0)/ 25 (18.1)/ 3 (1.4)	26 (32.9)/ 35 (44.3)/ 12 (15.2)/ 4 (5.1)	ns
Paid work (yes/no/missing)	48 (34.8)/ 89 (64.5)/ 1 (0.7)	37 (46.8)/ 40 (50.6)/ 2 (2.5)	ns
Clinical			
Type of surgery (BCT/MTC)	77 / 64	30 / 49	.017
BCT	17 (12.3)	23 (29.1)	
MTC	41 (29.7)	23 (29.1)	
Excision and sentinel node	60 (43.5)	7 (8.9)	
Ablation and sentinel node	20 (14.5)	26 (32.9)	
Adjuvant therapy*			
Chemotherapy (yes/no)	32 (23.2)/ 105 (76.1)	28 (35.4)/ 51 (64.6)	ns
Hormone therapy (yes/no)	45 (32.6)/ 93 (67.4)	40 (50.6)/ 39 (49.2)	.003
Radiotherapy (yes/no)	81 (58.7)/ 57 (41.3)	36 (45.6)/ 43 (54.4)	ns
Disease stage: 0 / I / IIa / IIb	12 (8.7)/ 71 (51.4)/ 37 (26.8)/18 (13.0)	12 (15.2)/ 20 (25.3)/ 30 (38.0)/ 17 (21.5)	.002
Psychological			
Overall QOL/General Health	15.5 ± 2.6	16.0 ± 2.3	ns
Depressive symptoms	15.2 ± 9.5	14.1 ± 9.5	ns
Fatigue	20.2 ± 6.9	18.7 ± 6.5	ns
Anxiety	47.8 ± 13.7	47.8 ± 14.2	ns

Abbreviations: BCT = breast conserving therapy, MTC = mastectomy, QOL = quality of life

Note: * more than one treatment possible, percentages are presented between brackets

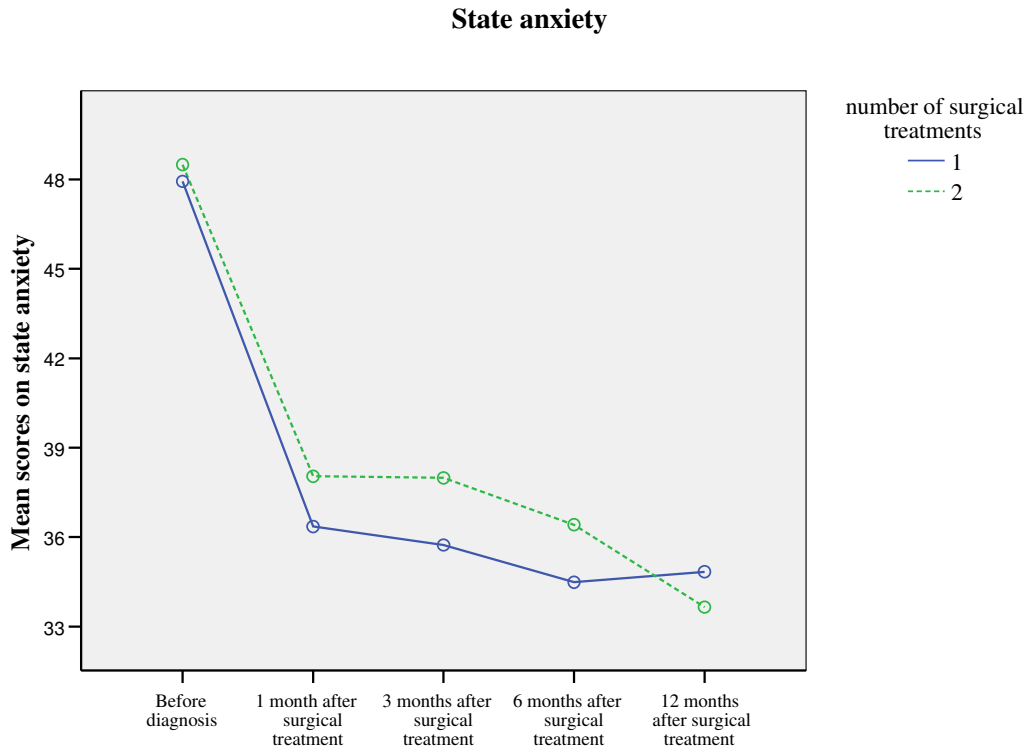
Table 2. Effects of time for psychological outcomes

	Wilks' Lambda	F-value	p-value	Partial eta squared	Observed power
Fatigue	.73	F(4,102) = 9.51	<.0001	.27	1.00
Anxiety	.38	F (4, 89) = 36.05	<.0001	.62	1.00
Depressive symptoms	.78	F(4,106) = 7.51	<.0001	.22	.99
Overall QOL and General Health	.93	F(4,110) = .07	.07	.07	.63
Physical Health	.87	F(4,110) = 4.09	.004	.13	.91
Psychological Health	.88	F(4,110) = 3.49	.01	.11	.85

Abbreviations: QOL = Quality of Life

Women with one or two surgical treatments did not differ on symptoms of anxiety [$F(1,92) = .013$, $p = .91$). However, an effect for time was found, indicating a decrease in symptoms of anxiety over time (see Figure 2). Mean scores of state anxiety scores at Time-1 were statistically different from scores at subsequent time points ($p<.0001$). In addition, scores on Time-2 (37.00 ± 11.26) were different from scores on Time-5 (34.38 ± 10.63, $p = .047$). No relationship was found between time and number of surgical treatment. After controlling for possible confounders, the effect for time remained significant [Wilks' Lambda = .72, $F(4,86) = 8.55$, $p<.0001$, partial eta squared = .29, observed power = 1.00].

Figure 2. Mean scores on state anxiety. Women were divided in two groups, according to the number of surgical treatments received. Higher scores indicate higher levels of anxiety.



Women with one and women with two surgical treatments did not differ on symptoms of depressive symptoms [$F(1,109)=.14$, $p=.71$, partial eta squared = .001, observed power = .07). Concerning depressive symptoms, an effect for time was found, indicating that depressive symptoms decrease over time. Mean scores of depressive symptoms at Time-1 (14.54 ± 9.61) were statistically different from Time-4 (11.68 ± 10.25, $p= .02$) and Time-5 (10.31 ± 8.50, $p<.0001$). Mean scores at Time-5 were also different from Time-2 (13.08 ± 9.78, $p=.001$) and Time-3 (12.63 ± 9.95, $p=.003$). No interaction effect was found. After controlling for possible confounders, the effect for time did not remain significant [Wilks'

Lambda =.93, $F(4,103) = 1.94$, p=.11, partial eta squared =.07, observed power = .57].

Concerning Overall QOL and General Health, no effect for time was found. No interaction effect (time *by* number of surgical treatments) was found, showing that the number of surgical treatments exerted a stable effect on Overall QOL and General Health scores. Women with one or two surgical treatments did not differ on symptoms of Overall QOL and General Health [$F(1,113)$=.59, p = .45, partial eta squared = .01, observed power = .12]. However, the univariate approach produced different results. Using the Greenhouse-Geiser estimates of sphericity (ε = .90), an effect for time was found [$F(3.59, 405.18) = 3.23$, p<.05)].

With regard to Physical Health, women with one or two surgical treatments did not differ on Physical Health [$F(1,113)$=.36, p = .55, partial eta squared = .03, observed power = .09]. An effect for time was found, indicating that Physical Health increases over time. Mean scores of Physical Health scores at Time-5 (14.60 ± 2.51) were statistically different from scores at Time-2 (14.04 ± 2.46; p=.006) and Time-4 (14.08 ± 2.42; p=.016). No interaction effect (time *by* number of surgical treatments) was found, showing that the number of surgical treatments exerted a stable effect on Physical Health scores. After controlling for possible confounders, the effect for time did not remain significant [Wilks' Lambda = .97, $F(4, 107) = .72$, p=.58, partial eta squared = .03, observed power = .26].

Women with one or two surgical treatments did not differ on Psychological Health [$F(1,114)$= .98, p = .33, partial eta squared = .01, observed power = .17]. Again an effect for time was found, this time indicating that Psychological Health improved over time. Mean scores of Psychological Health scores at Time-5 (15.35 ± 2.02) were statistically different from scores at Time-1 (14.81 ± 1.93; p<.05), Time-2 (14.89 ± 2.03; p<.01), and Time-3 (15.02 ± 2.04; p<.05). No interaction effect (time *by* number of surgical treatments) was found, showing that the number of surgical treatments exerted a stable effect on Psychological Health scores. After controlling for possible confounders, the effect for time did not remain significant [Wilks' Lambda = .96, $F(4, 108) = .1.21$, p = .31, partial eta squared = .04, observed power = .37].

Discussion

In the Netherlands, there is a fierce debate about the number of re-excisions in women with BC. The Inspection for Health Care suggested that, as a rule of thumb, 1 out of 10 women may get a second surgical treatment. Besides the costs associated with additional surgery, it is also speculated that women who get additional surgery will have, at least initially, more stress. However, no study has documented the effect of the number of surgical treatments on psychological outcomes. Does the group of women with more than one surgical treatment have more psychological problems than women who received just one operation? Therefore, the aim of this prospective follow-up study was to examine potential differences between women who received one surgical treatment and women who received two surgical treatments. This study showed that, in general, both groups did not differ on psychological outcomes, such as depressive symptoms and anxiety, over time. In addition, scores on depressive symptoms, anxiety, and fatigue initially decreased over time when we did not control for clinical factors. With regard to Overall QOL and General Health, the opposite trend was found. However, when adjuvant therapy and type of surgery were taken into account, these time effects disappeared. The effect for time remained present with regard to Physical Health.These findings may seem counter-intuitive at first glance. However, several explanations are suggested here. The fact that some women in our study needed an additional surgical treatment may not be easy for women initially. However, women may also realize that an extra surgery is for their own benefit. Irrespective of the number of surgical treatment, the aim is to remove malignant tissue from the body. Another explanation may be that the data set is somewhat biased. For instance, women with more than an additional surgical treatment tend to drop out more often from the study compared with women with one surgery. However, this suggestion was not supported by our findings (results not shown). Both groups did not differ on whether they drop out or the moment they dropped out from our study ($p>.24$).

This study has several limitations. First, women who receive multiple surgical treatments may vary in the type of treatment performed. However, as we used a rather small sample, it was not possible to divide the sample and examine whether women who received, for instance, BCT twice or women who were

converted from BCT to MTC differ in psychological functioning. Thus, our analyses were performed on a rather heterogeneous group. It would be interesting for future studies to further address this issue. Second, this study focused on psychological outcomes after surgical treatment. Therefore, no information is present on whether women with a repeated surgical treatment score differently on clinical physical outcomes compared with women who were operated only once. In order to partly overcome this limitation, we have assessed women on the WHOQOL-100-domain Physical health. Based on this self-evaluation, no differences were found between women operated once and women operated twice. Third, the time points were chosen in such a way that the follow-up measures would not interfere with the time of the treatment modalities. As a consequence, the timing of the second measurement point is dependent of the last surgical treatment, which is different in both surgical groups. Thus, information on psychological outcomes after the first surgical treatment is lacking. However, since, both groups do not differ at one month after surgical treatment, we may conclude that potential differences at that point were not long-lasting, since no differences were found at all measurement points.

In conclusion, women with early stage BC receiving multiple surgical treatments do not have worse psychological outcomes compared with women with one surgical treatment.

References

1. McPherson K, Steel CM, Dixon JM. ABC of breast diseases: Breast cancer---epidemiology, risk factors, and genetics. BMJ 2000;321:624-628.
2. Europäische Kommission [European Comittee]. Die Gesundheitssituation in der Europäischen Union (The health situation in the European Union). Amt fur amtliche Veröffentlichungen der Europäischen Gemeinschaften. Luxemburg; 2003.
3. Poortmans PMP. Quality assurance in clinical trials in breast cancers. Herentals, België: Drukkerij Bulckens NV; 2005.
4. Coebergh JWW, Janssen-Heijnen MLG, Voogd AC, Louwman WJ, editors. Cancer: Incidence, care and survival in the south of the Netherlands. Eindhoven, The Netherlands: Comprehensive Cancer Centre South (IKZ); 2001.
5. Waljee JF, Hu ES, Newman LA, Alderman AK. Predictors of re-excision among women undergoing breast-conserving surgery for cancer. Ann Surg Oncol 2008;15:1297-1303.
6. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233-1241.
7. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227-1232.
8. Ganz PA, Schag AC, Lee JJ, Polinsky ML, Tan SJ. Breast conservation versus mastectomy. Is there a difference in psychological adjustment or quality of life in the year after surgery? Cancer 1992;69:1729-1738.
9. King MT, Kenny P, Shiell A, Hall J, Boyages J. Quality of life three months and one year after first treatment for early stage breast cancer: influence of treatment and patient characteristics. Qual Life Res 2000;9:789-800.

10. Yurek D, Farrar W, Andersen BL. Breast cancer surgery: comparing surgical groups and determining individual differences in postoperative sexuality and body change stress. J Consult Clin Psychol 2000;68:697-709.
11. Holmberg L, Omne-Ponten M, Burns T, Adami HO, Bergstrom R. Psychosocial adjustment after mastectomy and breast-conserving treatment. Cancer 1989;64:969-974.
12. Fallowfield LJ. Psychosocial adjustment after treatment for early breast cancer. Oncology (Williston Park) 1990;4:89-97; discussion 97-8, 100.
13. Al-Ghazal SK, Fallowfield L, Blamey RW. Comparison of psychological aspects and patient satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. Eur J Cancer 2000;36:1938-1943.
14. Rijken M, de Kruif AT, Komproe IH, Roussel JG. Depressive symptomatology of post-menopausal breast cancer patients: a comparison of women recently treated by mastectomy or by breast-conserving therapy. Eur J Surg Oncol 1995;21:498-503.
15. Bani MR, Lux MP, Heusinger K, Wenkel E, Magener A, Schulz-Wendtland R, et al. Factors correlating with reexcision after breast-conserving therapy. Eur J Surg Oncol 2009;35:32-37.
16. Keskek M, Kothari M, Ardehali B, Betambeau N, Nasiri N, Gui GP. Factors predisposing to cavity margin positivity following conservation surgery for breast cancer. Eur J Surg Oncol 2004;30:1058-1064.
17. Fleming FJ, Hill AD, Mc Dermott EW, O'Doherty A, O'Higgins NJ, Quinn CM. Intraoperative margin assessment and re-excision rate in breast conserving surgery. Eur J Surg Oncol 2004;30:233-237.
18. O'Sullivan MJ, Li T, Freedman G, Morrow M. The effect of multiple reexcisions on the risk of local recurrence after breast conserving surgery. Ann Surg Oncol 2007;14:3133-3140.
19. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385-401.
20. Hann D, Winter K, Jacobsen P. Measurement of depressive symptoms in cancer patients: evaluation of the Center for Epidemiological Studies Depression Scale (CES-D). J Psychosom Res 1999;46:437-443.

21. De Rijk AE, Schreurs KMG, Bensing JM. What is behind "i'm so tired"? fatigue experiences and their relations to the quality and quantity of external stimulation. J Psychosom Res 1999;47:509-523.
22. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. Psychol Med 1997;27:231-235.
23. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: the Fatigue Assessment Scale. J Psychosom Res 2003;54:345-352.
24. De Vries J, Michielsen H, Van Heck GL, Drent M. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). Br J Health Psychol 2004;9:279-291.
25. Michielsen HJ, De Vries J, Drent M, Peros-Golubicic T. Psychometric qualities of the Fatigue Assessment Scale in Croatian sarcoidosis patients. Sarcoidosis Vasc Diffuse Lung Dis 2005;22:133-138.
26. Michielsen H, De Vries J, van Heck GL, Van de Vijver A, Sijtsma K. Examination of the dimensionality of fatigue: the construction of the Fatigue Assessment Scale (FAS). Eur J Psychol Assess 2004;20:39-48.
27. Van der Ploeg HM, Defares PB, Spielberger CD. ZBV: a Dutch-language adaptation of the Spielberger State-Trait Anxiety Inventory. Lisse, The Netherlands: Swets & Zeitlinger; 1980.
28. WHOQOL Group. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc Sci Med 1998;46:1569-1585.
29. De Vries J, Van Heck GL. The World Health Organization Quality of Life assessment instrument (WHOQOL-100): validation study with the Dutch version. Eur J Psychol Assess 1997;13:164-178.
30. Power M, Harper A, Bullinger M. The World Health Organization WHOQOL-100: tests of the universality of Quality of Life in 15 different cultural groups worldwide. Health Psychol 1999;18:495-505.
31. Den Oudsten BL, Van Heck GL, Van der Steeg AF, Roukema JA, De Vries J. The WHOQOL-100 has good psychometric properties in breast cancer patients. J Clin Epidemiol 2009;62:195-205.

32. O'Carroll RE, Smith K, Couston M, Cossar JA, Hayes PC. A comparison of the WHOQOL-100 and the WHOQOL-BREF in detecting change in quality of life following liver transplantation. Qual Life Res 2000;9:121-124.
33. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum; 1988.

Chapter 6

Personality predicts perceived availability of social support and satisfaction with social support in women with early stage breast cancer*

* Den Oudsten BL, Van Heck GL, Van der Steeg AFW, Roukema JA, De Vries J. Personality predicts perceived availability of social support and satisfaction with social support in women with early stage breast cancer. (Submitted for publication)

Abstract

Objective: This study examines the relationships between personality, on the one hand, and perceived availability of social support (PASS) and satisfaction with received social support (SRSS), on the other hand, in women with early stage breast cancer (BC). In addition, this study examined whether a stressful event (i.e. diagnosis) is associated with QOL, when controlling for PASS and SRSS. *Method:* Women were assessed on PASS and SRSS (WHOQOL-100) before diagnosis (Time-1) and one (Time-2), three (Time-3), six (Time-4), 12 (Time-5) and 24 months (Time-6) after surgical treatment. Personality (NEO-FFI, STAI-trait scale) and fatigue (FAS) were assessed at Time-1. *Results***:** Agreeableness and fatigue predicted PASS and SRSS at Time-5 and Time-6. Trait anxiety had a negative effect on SRSS (ß= -.22, $p<.05$). In addition, having a job was negatively associated with SRSS (Time-6, ß= -.23, $p<.001$). Across time, women reported a decrease in PASS and SRSS. Path models, used to test whether PASS and/or SRSS functioned as mediators of the link between diagnosis and QOL, reached adequate fit. *Conclusions***:** Besides factors, like fatigue and having a job, personality factors substantially influence the way women with early stage BC perceive social support. Knowledge about these underlying mechanisms of social support is useful for the development of tailor-made interventions. Professionals should be aware of the importance of social support. They should check whether patients have sufficient significant others in their social environment and be sensitive to potential discrepancies patients might experience between availability and adequacy of social support.

Introduction

In the Netherlands, over 11,500 women received a breast cancer (BC) diagnosis in 2003 [1]. In 2005, there were an estimated number of 119,000 BC patients or survivors in the Netherlands. Due to advances in cancer screening and medical treatment, this number might increase to about 194,000 within ten years [2]. In spite of these better prospects, receiving a BC diagnosis is still very stressful. For instance, BC patients have a high risk of developing mood disorders [3]. Therefore, social support from a partner, family, and/or friends is of the utmost importance for women with BC [4].

Despite a growing interest in social support, a precise definition is currently lacking. In general, there are two broad ideas: social support concerns (i) the support that is actually received (i.e., structural support, functional support) or (ii) the individual's subjective appraisal of the social support (perceived social support). Perceived social support can be divided into the perception that social support is available when needed (perceived availability of social support; PASS) and the satisfaction with received social support (SRSS). This approach is used in the current study.

Several studies have examined perceived social support in cancer. For instance, Hann et al. [5] reported that greater perceived adequacy of social support among cancer patients was negatively related to depression. With regard to the relationship between perceived social support and survival, findings are rather inconclusive. Whereas some studies [6-8] found a positive relationship between perceived social support and survival, others did not [9]. Social support is also associated with quality of life (QOL) in BC patients [10-15]. Socially isolated women reported more problems compared with women who were socially integrated with regard to physical role functioning, vitality, and physical functioning [15]. Thus, social support seems to fulfil an important role in adaptation efforts of cancer patients.

In order to understand the underlying mechanisms of the protective role of perceived social support, it is important to examine its determinants or the factors associated with it [16]. Few studies have tested those determinants longitudinally [17]. Objective determinants, such as, network size or the frequency of contact with network members, explained about 30% of the variance

of perceived social support [16]. In addition, perceived social support may also be associated with other factors, for instance, personality. Few studies, however, have examined this particular relationship [18]. Research has shown that extraverts report higher scores on satisfaction with the social support they receive compared with introverts [19, 20]. A longitudinal study among alcoholics [21] found that extraversion and neuroticism were indirectly related to perceived social support through their effects on network properties during treatment. Furthermore, it was demonstrated that agreeableness, i.e., the tendency towards interpersonal trust and consideration of others, predicts actual support from others [20]. Recently, Hoth et al. [22] studied agreeableness in persons with chronic kidney disease. Persons high on agreeableness showed a substantial decrease in depressive symptoms across time, while support had little effect for low-scorers. In another study [4] dispositional optimism and perceived social support were substantially related to well-being. In addition, women who were not treated yet and scored low on dispositional optimism experienced more cancer-specific distress. Persons high on trait anxiety were inclined to seek more support from others, while they also tended to be dissatisfied with the received social support [23, 24]. Courtens et al. [17] found that network size decreased over time. Since their illness, cancer patients were relatively less able to provide support to their social network, which caused an imbalance between the amount of support given to others and the amount of help received by the network. Presumably, this imbalance had a negative impact on their social network. However, there is still a limited body of knowledge regarding the question whether, in line with a decreasing social network, perceived social support also diminishes across time, since the remaining support providers may give the support patients need.

Therefore, the aim of this prospective longitudinal follow-up study was to examine the relationships between personality and PASS and SRSS in early stage BC patients. In addition, we examined whether PASS and/or SRSS mediates the link between diagnosis and QOL. Based on earlier findings, it was hypothesized that women scoring high on extraversion and agreeableness would experience higher perceived availability and higher scores on satisfaction compared with women scoring low or moderately on these traits. Furthermore, it was expected that high scores on neuroticism and trait anxiety would be negatively associated with PASS and SRSS. Moreover, it was hypothesized that the levels of PASS and

SRSS would be high in the period around surgical treatment and then, subsequently, would decline. It was expected that women scoring high on trait anxiety would be less satisfied with their social support. It was expected that women scoring high on trait anxiety would be less satisfied with their social support at all time points, compared to women with low or moderate scores. Finally, it was expected that PASS and SRSS are mediators of the link between diagnosis and QOL.

Method

Participants

Women with a palpable lump in the breast or an abnormality on a screening mammography were referred by their general practitioner to the surgical outpatient clinics of the St. Elisabeth Hospital (Tilburg, The Netherlands), the Maasland Hospital (Sittard, The Netherlands; since August 2004), or the Jeroen Bosch Hospital (Den Bosch, The Netherlands; since January 2006). The present study, in which PASS and SRSS is examined, is part of a large study focusing on the role of personality in early stage BC patients' QOL. The data were collected from September 2002 until September 2006. Of the 799 eligible women, 604 (75.6%) completed the first set of questionnaires. The main reasons for not participating were the length of the test battery and the amount of stress women experienced at their first visit to the hospital. Of these 604 women, 223 were diagnosed with early stage breast cancer (BC; see Figure 1). A substantial number of women had benign breast problems (BBP; n = 381). Women who had a history of abnormalities in the breast, benign or malignant, or had a breast tumor that was too large (>5 centimeter) for breast conserving therapy, were excluded from the study. In order to participate, the women had to have sufficient knowledge of the Dutch language. The questionnaires were completed before the women visited the surgeon or radiologist, i.e. *before* the diagnosis, benign or malignant, was known. After the baseline measurement (Time-1), women completed questionnaires at one (Time-2), three (Time-3), six (Time-4), 12 (Time-5) and 24 (Time-6) months after surgical treatment. The reference point was surgical treatment, because otherwise follow-up measures would interfere with the timing of treatment modalities. Participation in the study was not known to the surgeon in attendance

and, therefore, could not affect treatment and clinical follow-up. All participants gave written informed consent.

Measures

Women completed the following questionnaires: World Health Organization Quality of Life assessment instrument-100 (WHOQOL-100) [25, 26] at all time points. The Center for Epidemiological Studies-Depression Scale (CES-D) [27], the Fatigue Assessment Scale (FAS) [28], the Neuroticism-Extraversion-Openness-Five Factor Inventory (NEO-FFI) [29, 30] and the State Trait Anxiety Inventory (STAI) [31] were assessed at Time-1.

Social support and General Health and Overall Quality of Life were measured using the WHOQOL-100 [26, 32]. Each facet is measured with four items with a 5-point Likert scale. High scores on these facets indicate good QOL. Reliability and validity [32-34] are adequate, and sensitivity [35] of the instrument is high. For instance, Cronbach's alpha for the facet Social Support exceeds .80 [34]. This facet consists of four items: (i) Do you get the kind of support from others that you need? (item 43), (ii) To what extent can you count on your friends when you need them? (item 44), (iii) How satisfied are you with the support you receive from your family? (item 66), and (iv) How satisfied are you with the support you receive from your friends (item 67)? In this study, we calculated two subscores by adding the scores of the first two items in order to measure PASS (α = .68), and the total scores of the last two items in order to measure SRSS (α = .73). The time frame of reference is the previous two weeks.

The CES-D [27] is a 20-item self-report scale designed to measure the presence and degree of depressive symptoms over the past week. The rating scale ranges from 0 (*seldom or never)* to 3 (*(almost) always*). Scores can range from 0 to 60. The CES-D has been established as a valid and reliable measure of depressive symptoms in BC patients [36]. For the Dutch population, reliability and criterion validity are good [37, 38].

The FAS [28] is a 10-item questionnaire assessing a uni-dimensional construct of perceived fatigue and exhaustion. The response scale is a 5-point rating scale ranging from 1 (*never*) to 5 (*always*). Scores on the FAS range from 10 to 50. The psychometric properties are good [39-41].

Personality was assessed with the NEO-FFI [29, 30] and the State-Trait Anxiety Inventory (STAI) [31, 42]. The NEO-FFI has been translated into Dutch [43]. This self-report questionnaire consists of 60 statements covering five basic dimensions of personality: Neuroticism, Extraversion, Openness to New Experiences, Agreeableness, and Conscientiousness. Each statement is rated on a 5-point scale ranging from 1 (*strongly disagree*) to 5 (*strongly agree*), resulting in dimension scores between 12 and 60. The psychometrics of the NEO-FFI have been extensively examined. The internal consistency, test-retest reliability, as well as the convergent validity, are acceptable to good [43].

The STAI [31, 42] consists of two 20-item scales for measuring state anxiety and trait anxiety. In this study, the STAI trait scale was used. This scale describes how persons *generally* feel and refers to their inclination to experience anxiety in stressfull times. The STAI has a 4-point rating scale ranging from 1 (*not at all/almost never*) to 4 (*very much so/almost always*). The Dutch version of the STAI has good reliability and validity [42].

Socio-demographic and clinical variables

Patients were asked to report age, marital status, education, and paid work (*yes/no*). Clinical variables, for instance, adjuvant therapy, were retrieved from medical files.

Statistical procedure

Pearson correlation coefficients were used to examine the relationship between PASS and SRSS, on the one hand, and the independent variables (sociodemographic and personality), on the other hand. Multiple linear regression analyses (method: enter) were performed to identify factors associated with PASS and SRSS at Time-5 and Time-6. First, the sets of socio-demographic, clinical, personality, and psychological characteristics were entered separately in the regression analyses. This procedure was employed to minimize the number of independent variables in the final regression analysis preserving statistical power. Subsequently, only those factors that significantly ($p<.05$) predicted the dependent variables were entered in the final analyses. General linear model analysis was used to examine PASS and SRSS across time. This was done until Time-5, due to the rather limited sample size at Time-6. However, this limited

sample size was not a problem in the regression analysis. Partial eta squared (effect size) was derived from the general linear model. An effect size between 0.01 and 0.06 is considered as a small effect, while effect sizes between 0.06 and 0.13 and greater than 0.14 are considered as moderate and strong effect sizes, respectively [44]. Multiple post hoc comparisons were corrected with the Bonferroni method. Path analyses were conducted to test whether PASS and/or SRSS are mediators of the relationship between stress and QOL [45]. In this study, the hypothesized models were tested at each measurement point (Time-2 to Time-5). In the model, the latent variable 'stress' was linked to the diagnosis women had received. Therefore, only in these analyses women with BC and BBP were used. As outlined above, the PASS and SRSS latent variables were both measured with two observed indicators. In the hypothesized models, stress was specified as the predictor, PASS and SRSS were conceived as mediators, and QOL was specified as the outcome. To evaluate the model, multiple indices of fit were used, including: an overall chi-square statistic, the comparative fit index (CFI), and the root mean square error approximation (RMSEA). The models have a satisfactory to good fit when: CFI > .90 and RMSEA < .06 [46]. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Chicago, IL, USA; version 14.0), except for the path analyses. These analyses were performed using Analysis of Moment Structures (AMOS; version 7.0)

Results

In total, 799 patients were eligible for this study. Before diagnosis was known, 609 (76.2%) completed the first set of questionnaires before they visited the surgeon or radiologist. Participants were significantly younger compared with non-participants (p =.002). Participants and non-participants did not differ on other sociodemographic or clinical characteristics. Figure 1 shows the flow chart of this study. The outcomes regarding the socio-demographic, clinical, and psychological characteristics are presented in Table 1. Women with BBP were younger [t (1, 603) = -6.81, p < 0.001) and more often employed (χ^2 = 11.46, p = 0.001) compared with the BC group.

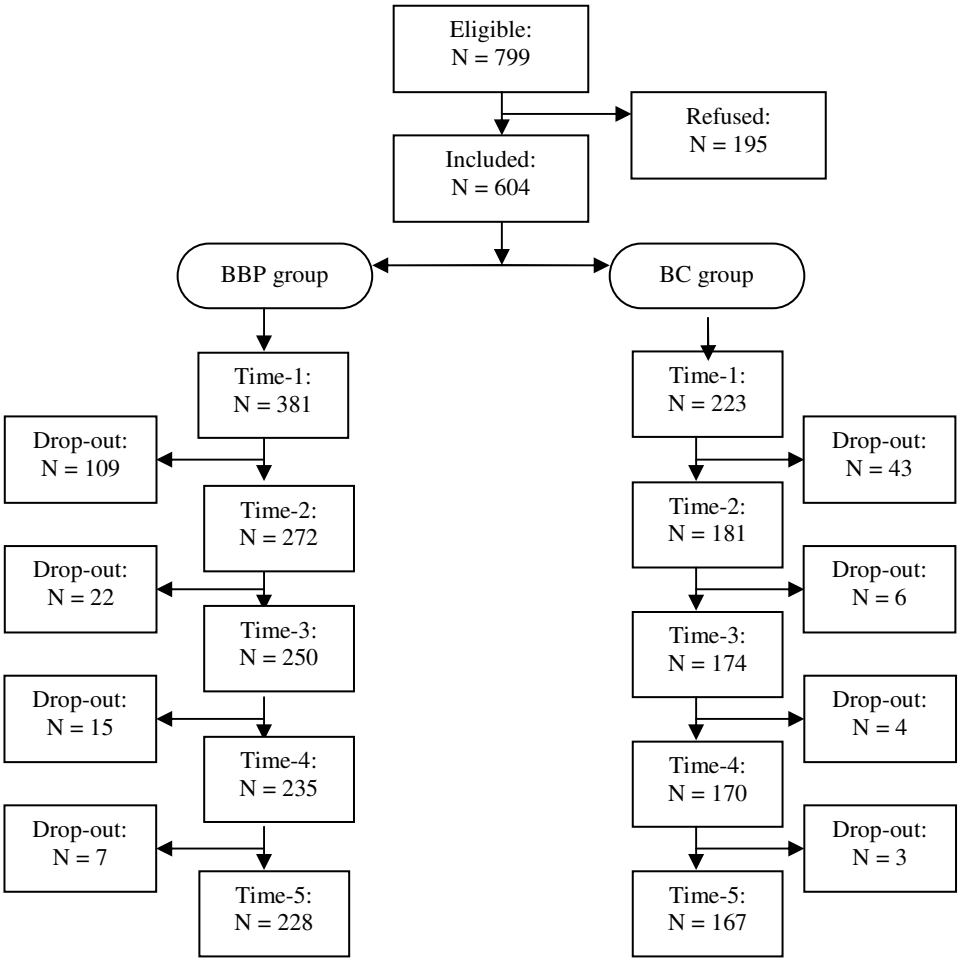
Table 1. Demographic, clinical, personality, and psychological characteristics at baseline

	BC group (n = 223)
Sociodemographic factors	
Age at diagnosis (mean ± SD)	58.7 (9.4)
Living with a partner (*yes /no /missing*)	179 (80.3) / 37 (16.6) / 3 (1.3)
Having children (*yes / no / missing*)	191 (85.7) / 29 (13.0) / 3 (1.3)
Education level:	
0-9 yrs / 10-14 yrs / > 14 years /missing	85 (38.1) / 95 (42.6) / 37 (16.6) / 2 (0.9)
Paid work *(yes / no / missing)*	85 (38.1) / 135 (60.5) / 1 (0.4)
Clinical factors	
Disease stage	
Stage 0 / Stage I	24 (10.8) / 93 (41.7)
Stage IIa / Stage IIb	69 (30.9) / 35 (15.7)
Undefinable	2 (0.9)
Type of surgery:	
BCT / MTC / No surgical treatment	107 (48.0) / 114 (51.1) / 2 (0.9)
Adjuvant therapy (*yes / no*)	169 (75.8) / 54 (24.2)
Personality factors	
Neuroticism	30.2 (7.0)
Extraversion	41.1 (5.5)
Openness to New Experiences	35.4 (6.0)
Agreeableness	43.5 (4.1)
Conscientiousness	45.5 (5.4)
Trait Anxiety	39.4 (11.0)
Depressive symptoms	14.9 (9.5)
Fatigue	19.8 (9.5)

Abbreviations: MTC = modified radical mastectomy; BCT = breast conserving therapy

Note: For the sociodemographics, percentages are presented between brackets (except for age). For the personality and psychological factors the means and standard deviations (SD) are presented.

Figure 1. Flow chart for the recruitment of women with breast problems.
BBP = benign breast problems, *BC* = breast cancer



Neuroticism and trait anxiety were negatively associated with both PASS and SRSS, while extraversion, conscientiousness, and agreeableness were positively associated with these aspects of social support (Table 2). Correlation coefficients in Table 2 relate to Time-1.

Table 2. Pearson correlation coefficients between perceived social support, age, and personality characteristics

Variables	PASS (Time-1)	SRSS (Time-1)
Age	.01	-.06
Neuroticism	-.19**	-.22**
Extraversion	.20**	.30**
Openness to New Experiences	.08	.17
Agreeableness	.26**	.26**
Conscientiousness	.16 *	.12 *
Trait anxiety	-.18**	-.22**

Note: * p<.05, ** p <.01 (2-tailed tested)

Trait anxiety (ß = -.22, p = .021), agreeableness (ß = .29, p < .0001), and fatigue (ß = -.21, p < .008) predicted SRSS at Time-5. These factors also contributed significantly to the prediction of PASS at Time-5, except for trait anxiety. At Time-6, agreeableness as well as fatigue predicted PASS and SRSS. In addition, having a job was negatively associated with SRSS (ß = -.23, p < .001) (Table 3).

Table 3. Significant predictors of PASS and SRSS at Time-5 and Time-6

	Time	Predictors	Adjusted R^2 total	Beta	F-value
PASS	Time-5	Agreeableness	.219	.274**	13.594 †
		Fatigue		-.263 *	
SRSS	Time-5	Trait anxiety	.278	-.221 *	18.351†
		Agreeableness		.291 †	
		Fatigue		-.206 *	
PASS	Time-6	Agreeableness	.280	.313**	12.14†
		Fatigue		-.272 *	
SRSS	Time-6	Agreeableness	.375	.337 †	13.76†
		Fatigue		-.299**	
		Paid job (*yes/no*)		-.232**	

Abbreviations: PASS, perceived availability of social support; *SRSS,* satisfaction with received social support.

Note: †= p < .0001; ** = p < .001: * = p < .05

There was no effect of time on PASS scores for women scoring low or moderately on agreeableness versus high-scorers on this trait (p =.28). In addition, no interaction effect was found between time * agreeableness, showing that agreeableness exerted a stable effect on PASS over time (p = .73). However, low-scorers on agreeableness reported significantly poorer PASS (p = .001) compared to high-scorers (Figure 2).

In contrast, a significant effect across time was found with regard to SRSS scores and agreeableness (Wilks' Lambda = .88, $F(4,93) = 3.16$, $p = .017$, multivariate partial eta squared = .12; see Figure 3). No interaction effect was found between time * agreeableness, showing that agreeableness exerted a stable effect on SRSS over time (p = .47). The mean scores of social support at Time-2 were statistically different from the scores obtained at Time-4 ($p = .027$), indicating a significant decline. Women high on agreeableness had significantly higher scores on SRSS compared with women low or moderately on this trait ($F = 9.24$, $p = .003$, partial eta squared = .088).

Concerning trait anxiety, there was also a significant effect across time, indicating that SRSS decreased over time (Wilks' Lambda = .86, $F(4,137) = 4.14$, $p = .004$, multivariate partial eta squared = .14; see Figure 4). The mean scores of SRSS at Time-2 were statistically different from the scores obtained at Time-4 ($p = .008$) and Time-5 ($p = .005$), indicating a sizeable decline. In addition, women high on trait anxiety had significantly lower scores on SRSS compared with women low or moderately on trait anxiety ($F = 34.66$, $p < .0001$, partial eta squared = .25).

Figure 2. PASS scores of patients before diagnosis and one, three, six, and 12 months after surgical treatment. Women with early stage BC were divided in two groups, according to their scores on agreeableness (low or moderate versus high).

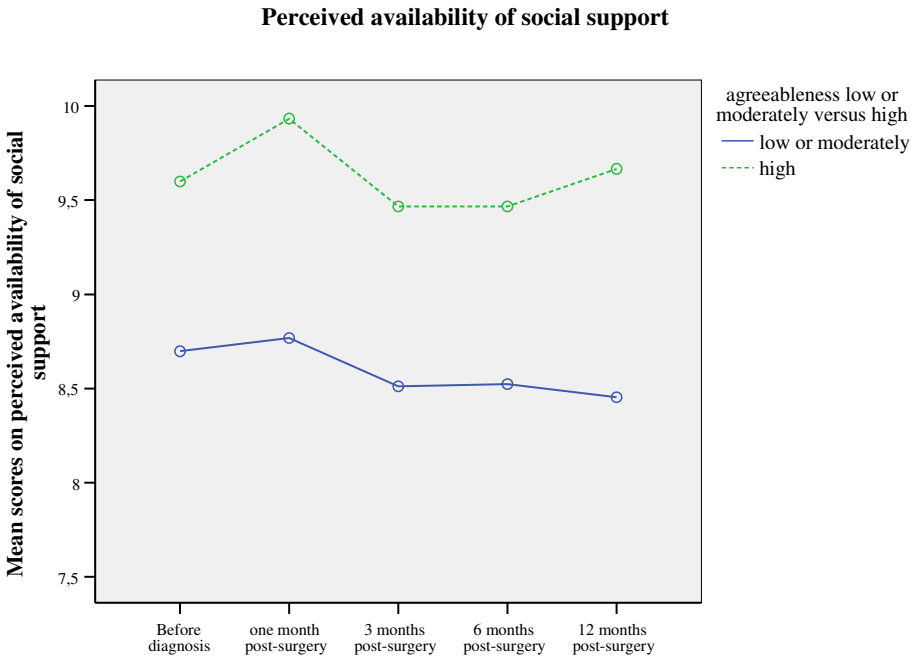


Figure 3. SRSS scores of patients before diagnosis and one, three, six, and 12 months after surgical treatment. Women with early stage BC were divided in two groups, according to their scores on agreeableness (low or moderate versus high).

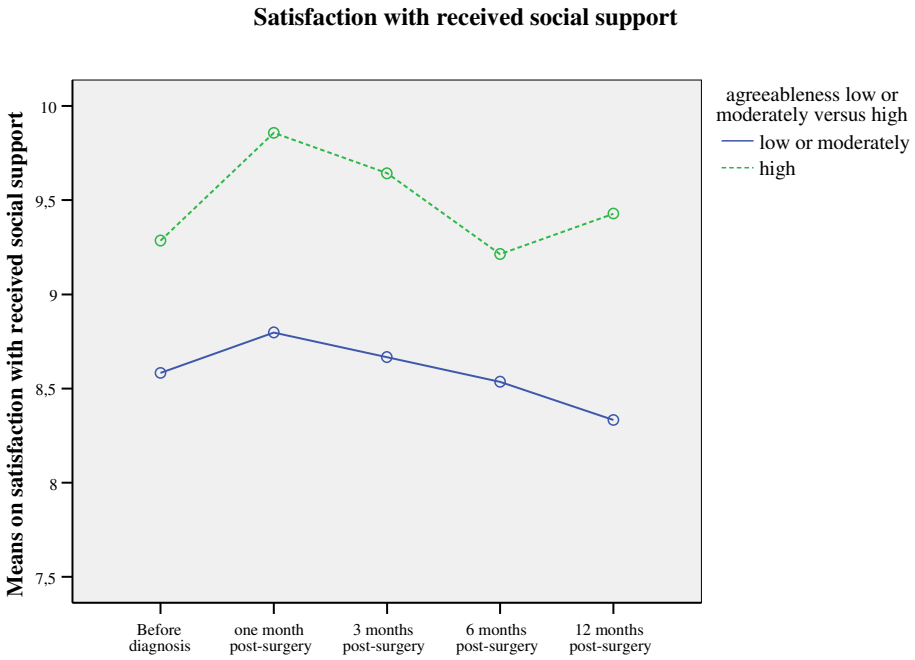


Figure 4. SRSS scores of patients before diagnosis and one, three, six, and 12 months after surgical treatment. Women with early stage BC were divided in two groups, according to their scores on trait anxiety (low or moderate versus high).

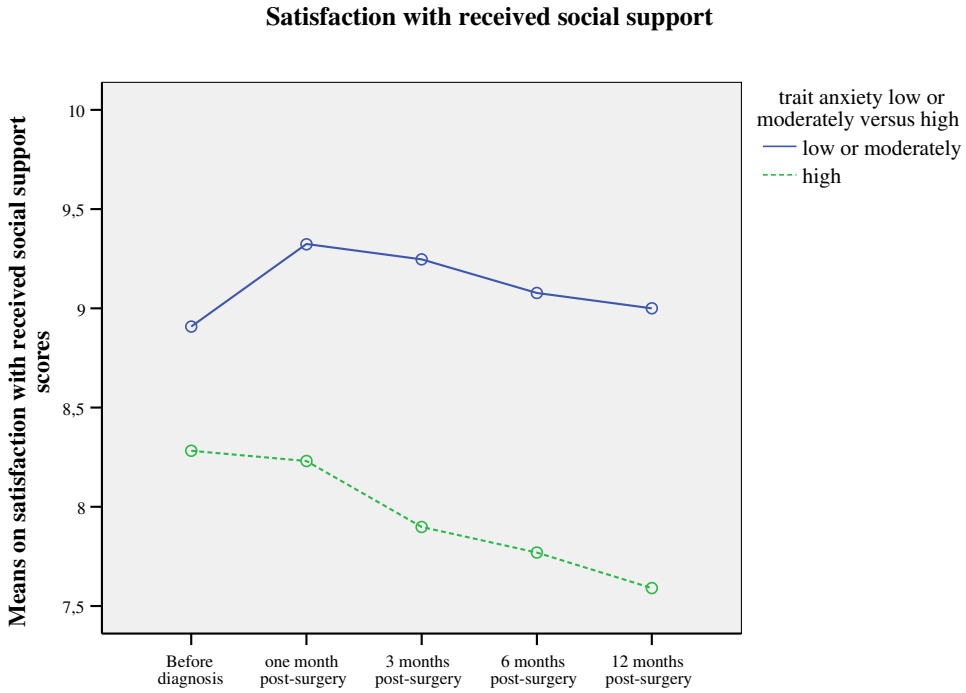


Figure 5 presents the path diagrams of the mediational models. These models were used to test whether PASS and/or SRSS functioned as a mediator of the relationship between diagnosis and overall QOL at different time points. To reach a better fit, the model required two correlations of two error terms for PASS from Time-2 to Time-4 (‘estimation of QOL’ with ‘stress’; ‘satisfaction with health’ with ‘stress’). Adding constrains was not necessary for reaching an adequate fit with regard to PASS at Time-5. To reach a better fit, the SRSS model required at least two correlations of two error terms (Time-2: ‘estimation of QOL’ with ‘stress’, ‘satisfaction with health’ with ‘stress’, ‘satisfaction with QOL’ with ‘satisfaction with support from family, Time-3: ‘satisfaction with life in general’ with ‘satisfaction with health’, ‘satisfaction with health’ with ‘stress’, ‘satisfaction with QOL’ with ‘stress’, ‘diagnosis’ with ‘satisfaction with support from friends’,

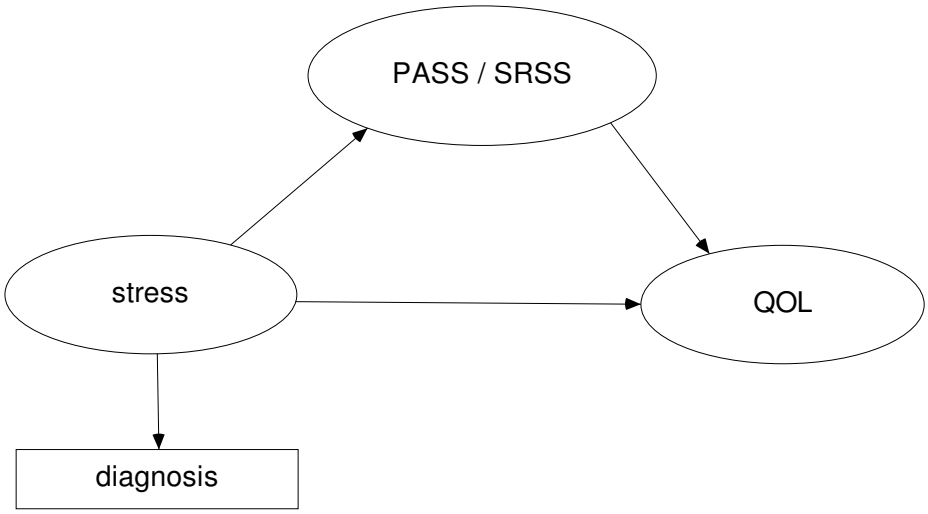
'Time-4: satisfaction with QOL' with 'stress' and 'satisfaction with health' with 'stress', Time-5: 'satisfaction with health' with 'satisfaction with support from family', 'satisfaction with health' with 'satisfaction with support from friends). A summary of the overall goodness-of-fit statistics of the path models and the added error variances are presented in Table 4. These models have a satisfactory fit.

Table 4. Longitudinal path model statistics

Model	Chi-square	p-value	df	CFI	RMSEA	Number of constraints
PASS, Time-1 to Time-2	8.877	.449	9	1.000	.000	2
PASS, Time-1 to Time-3	8.877	.449	9	1.000	.000	2
PASS, Time-1 to Time-4	9.483	.394	9	1.000	.000	2
PASS, Time-1 to Time-5	11.567	.481	12	1.000	.000	0
SRSS, Time-1 to Time-2	11.404	.180	8	.997	.038	3
SRSS, Time-1 to Time-3	12.132	.096	7	.995	.053	4
SRSS, Time-1 to Time-4	6.087	.731	9	1.000	.000	2
SRSS, Time-1 to Time-5	16.912	.076	10	.992	.054	2

Note: PASS, perceived availability of social support; SRSS, satisfaction with received social support; df, degrees of freedom; CFI, comparative fit index; RMSEA, root mean square residuals.

Figure 5. The path models for PASS and SRSS as mediator variables in the link between stress at diagnosis of early stage breast cancer and general quality of life across time. Ovals represent latent variables. In the interest of clarity, error terms are not shown. *PASS* = perceived availability of social support, *SRSS* = satisfaction with social support, *QOL* = quality of life. Stress was measured with the diagnosis women had received.



Discussion

The aim of this study was to examine the role of personality factors in PASS and SRSS in BC patients. Agreeableness was positively associated with perceived social support at Time-5 and Time-6. Several explanations can be given for this finding: (*i*) persons who are more agreeable may be more strongly motivated to maintain positive relationships with others compared with persons who are less agreeable [47); (*ii*) high-scores on agreeableness tend to interpret the behaviors of others more positively and also tend to react more positively upon them [48]. A consequence could be that persons scoring high on agreeableness tend to receive more support from others [49] compared with persons scoring low on this trait. At Time-5 and Time-6, trait anxiety was negatively associated with perceived social support. Persons scoring high on trait anxiety in general are more anxious. As a result, high-scorers will presumably seek more support from

significant others [23]. However, Hobson, Slade, Wrench, and Power [24] found that persons scoring high on trait anxiety tend to score lower on perceived social support, compared with persons scoring low on trait anxiety. In contrast with persons scoring high on agreeableness, persons scoring high on trait anxiety might interpret the behaviors of others more negatively and also tend to react more negatively upon others. Another explanation may be that high-anxious women are not easily reassured by others. Therefore, they never receive enough social support to feel at ease. At first glance, it seems a paradox that having a job (Time-6) is negatively associated with perceived social support, because women who work are usually surrounded by others. An explanation for this finding, however, may be that the environment tends to provide less support or provide support differently due to the fact that women who are working after two years of surgical treatment seem to pick up their 'normal' life. In this way, women with (former) BC present themselves to others as 'doing fine'. Although it may seem that women are fully functioning, they perceive the regular check-ups as stressful [50]. Across time, women with early stage BC report a decrease in perceived social support. Women scoring low or moderately on agreeableness or high on trait anxiety tend to score lower on perceived social support compared with women scoring high on agreeableness or low or moderately on trait anxiety across all time points.

Across time, scores of perceived social support significantly declined with respect to trait anxiety and agreeableness. High-scorers on trait anxiety or low-scorers on agreeableness tend to score lower on perceived social support. To what extent, however, social support is actually lower is not clear. To the best of our knowledge, no studies have related personality characteristics to perceived social support longitudinally. However, Courtens et al. studied social support across time and found that the size of the networks as well as the amount of emotional support showed some decrease over time [17].

The path models reached an adequate fit when examining the role of PASS and SRSS as mediating variables of the link between diagnosis and QOL. To the best of our knowledge, no existing studies examined the abovementioned relationship. In fact, few studies have examined relationships between social support and QOL. Recently, Lim and Zebrack [51] found that network diversity indirectly affected QOL through perceived social support.

As social support is an aspect of QOL, it seems important to try to increase its level. Potential problems with regard to perceived social support could be improved by, for instance, trying to involve the partner or family in the treatment plan. In this way, significant others are aware of the problems women with early stage BC are facing during and after the treatment process. Another option is to try to educate women with early stage BC and their families about the importance of social support, i.e., to teach women to ask for help, when they need support, or to learn how they can best discuss their needs, when they are not satisfied. Nevertheless, it is important to keep in mind that personality traits are quite stable. Also, the way persons encounter and perceive social situations is not easily altered.

The current study has a couple of limitations. For instance, the study population at Time-6 was rather small (n = 92). Therefore, we should be careful, when interpreting and generalizing the results based on this particular sample. Another limitation is that we only assessed perceived social support. As a consequence, it was not possible to examine whether the same or other sociodemographic and personality factors were related to more quantitative aspects of social support, for instance, network size or frequency of appointments. Information concerning the type of support (i.e., instrumental support and emotional support) women received and needed from significant others was also lacking. Thus, future studies should further examine the role of potential factors which play a role in social support and combine these findings with assessing the needs of women with early stage BC. In this way, screening and treatment can be geared to one another.

In conclusion, personality traits are important determinants of perceived social support. Understanding the underlying mechanisms of perceived social support will be useful in the development of interventions for women with BC.

References

1. Netherlands Cancer Registry. Most prevalent cancer types [Meest voorkomende kankersoorten]. In: http://www.ikcnet.nl/page.php?id=868& nav_id =114; 2005.
2. SignaleringscommissieKanker. Cancer in the Netherlands. Trends, prognosis, and implications for care demands [Kanker in Nederland. Trends, prognoses en implicaties voor zorgvraag]. KWF Kankerbestrijding; 2004.
3. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. BMJ 2005;330:702.
4. Friedman LC, Kalidas M, Elledge R, Chang J, Romero C, Husain I, et al. Optimism, social support and psychosocial functioning among women with breast cancer. Psycho-oncology 2006;15:595-603.
5. Hann D, Baker F, Denniston M, Gesme D, Reding D, Flynn T, et al. The influence of social support on depressive symptoms in cancer patients: age and gender differences. J Psychosom Res 2002;52:279-283.
6. Weihs KL, Enright TM, Simmens SJ. Close relationships and emotional processing predict decreased mortality in women with breast cancer: preliminary evidence. Psychosom Med 2008;70:117-124.
7. Weihs KL, Simmens SJ, Mizrahi J, Enright TM, Hunt ME, Siegel RS. Dependable social relationships predict overall survival in Stages II and III breast carcinoma patients. J Psychosom Res 2005;59:299-306.
8. Kroenke CH, Kubzansky LD, Schernhammer ES, Holmes MD, Kawachi I. Social networks, social support, and survival after breast cancer diagnosis. J Clin Oncol 2006;24:1105-1111.
9. Cassileth BR, Lusk EJ, Miller DS, Brown LL, Miller C. Psychosocial correlates of survival in advanced malignant disease? N Engl J Med 1985;312:1551-1555.
10. Manning-Walsh J. Social support as a mediator between symptom distress and quality of life in women with breast cancer. J Obstet Gynecol Neonatal Nurs 2005;34:482-493.

11. Lewis JA, Manne SL, DuHamel KN, Vickburg SM, Bovbjerg DH, Currie V, et al. Social support, intrusive thoughts, and quality of life in breast cancer survivors. J Behav Med 2001;24:231-245.
12. Ogce F, Ozkan S, Baltalarli B. Psychosocial stressors, social support and socio-demographic variables as determinants of quality of life of Turkish breast cancer patients. Asian Pac J Cancer Prev 2007;8:77-82.
13. Karnell LH, Christensen AJ, Rosenthal EL, Magnuson JS, Funk GF. Influence of social support on health-related quality of life outcomes in head and neck cancer. Head Neck 2007;29:143-146.
14. Sammarco A. Perceived social support, uncertainty, and quality of life of younger breast cancer survivors. Cancer Nurs 2001;24:212-219.
15. Michael YL, Berkman LF, Colditz GA, Holmes MD, Kawachi I. Social networks and health-related quality of life in breast cancer survivors: a prospective study. J Psychosom Res 2002;52:285-293.
16. Cutrona C. Objective determinants of perceived social support. J Person Soc Psychol 1986;50:349-355.
17. Courtens AM, Stevens FC, Crebolder HF, Philipsen H. Longitudinal study on quality of life and social support in cancer patients. Cancer Nurs 1996;19:162-169.
18. Roberts S, Wilson R, Fedurek P, Dunbar R. Individual differences and personal social network size and structure. Person Individ Dif 2008;44:954-964.
19. Swickert R, Rosentreter C, Hittner J, Mushrush J. Extraversion, social support, and stress. Person Individ Dif 2002;32:877-891.
20. Bowling N, Beehr T, Swader W. Giving and receiving social support at work: the roles of personality and reciprocity. J Vocat Behav 2005;67:476-489.
21. Russell D, Booth B, Reed D, Laughin P. Personality, social networks, and perceived social support among alcoholics: a structural equation analysis. J Pers 1997;65:649-692.
22. Hoth KF, Christensen AJ, Ehlers SL, Raichle KA, Lawton WJ. A longitudinal examination of social support, agreeableness and depressive symptoms in chronic kidney disease. J Behav Med 2007;30:69-76.

23. Deisinger J, Cassisi J, Withaker S. Relationships between coping style and PAI profiles in a community sample. J Clin Psychol 2003;59:1315-1323.
24. Hobson JA, Slade P, Wrench IJ, Power L. Preoperative anxiety and postoperative satisfaction in women undergoing elective caesarean section. Int J Obstet Anesth 2006;15:18-23.
25. WHOQOL group. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med 1995;41:1403-1409.
26. WHOQOL Group. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc Sci Med 1998;46:1569-1585.
27. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385-401.
28. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: the Fatigue Assessment Scale. J Psychosom Res 2003;54:345-352.
29. Costa PT, McCrae RR. The NEO Personality Inventory Manual. Odessa, FL: Psychological Assessment Resources Inc.; 1985.
30. Costa PT, McCrae RR. Revised NEO Personality Inventory (NEO-PI-R) and NEO Five Factor Inventory (NEO-FFI) professional manual. Odessa, FL: Psychological Assessment Resources Inc.; 1992.
31. Spielberger CD, Gorsuch RL, Lushene RE. STAI manual for the State-Trait Anxiety Inventory. Palo-Alto, CA: Consulting Psychologists Press; 1970.
32. De Vries J, Van Heck GL. The World Health Organization Quality of Life assessment instrument (WHOQOL-100): validation study with the Dutch version. Eur J Psychol Assess 1997;13:164-178.
33. Power M, Harper A, Bullinger M. The World Health Organization WHOQOL-100: tests of the universality of Quality of Life in 15 different cultural groups worldwide. Health Psychol 1999;18:495-505.
34. Den Oudsten BL, Van Heck GL, Van der Steeg AF, Roukema JA, De Vries J. The WHOQOL-100 has good psychometric properties in breast cancer patients. J Clin Epidemiol 2009; 62:195-205.

35. O'Carroll RE, Smith K, Couston M, Cossar JA, Hayes PC. A comparison of the WHOQOL-100 and the WHOQOL-BREF in detecting change in quality of life following liver transplantation. Qual Life Res 2000;9:121-124.
36. Hann D, Winter K, Jacobsen P. Measurement of depressive symptoms in cancer patients: evaluation of the Center for Epidemiological Studies Depression Scale (CES-D). J Psychosom Res 1999;46:437-443.
37. De Rijk AE, Schreurs KMG, Bensing JM. What is behind "i'm so tired"? fatigue experiences and their relations to the quality and quantity of external stimulation. J Psychosom Res 1999;47:509-523.
38. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. Psychol Med 1997;27:231-235.
39. De Vries J, Michielsen H, Van Heck GL, Drent M. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). Br J Health Psychol 2004;9:279-291.
40. Michielsen HJ, De Vries J, Drent M, Peros-Golubicic T. Psychometric qualities of the Fatigue Assessment Scale in Croatian sarcoidosis patients. Sarcoidosis Vasc Diffuse Lung Dis 2005;22:133-138.
41. Michielsen H, De Vries J, van Heck GL, Van de Vijver A, Sijtsma K. Examination of the dimensionality of fatigue: the construction of the Fatigue Assessment Scale (FAS). Eur J Psychol Assess 2004;20:39-48.
42. Van der Ploeg HM, Defares PB, Spielberger CD. ZBV: a Dutch-language adaptation of the Spielberger State-Trait Anxiety Inventory. Lisse, The Netherlands: Swets & Zeitlinger; 1980.
43. Hoekstra H, Ormel J, De Fruyt F. Handleiding NEO persoonlijkheidsvragenlijsten NEO-PI-R en NEO-FFI [manual NEO personality questionnaires NEO-PI-R and NEO-FFI]. Lisse, The Netherlands: Swets Test Services; 1996.
44. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum; 1988.

45. Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behav Res Methods Instrum Comput 2004;36:717-731.
46. Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Structural Equation Modelling 1999;6:1-55.
47. Jensen-Campbell LA, Graziano WG. Agreeableness as a moderator of interpersonal conflict. J Pers 2001;69:323-361.
48. Finch JF, Graziano WG. Predicting depression from temperament, personality, and patterns of social relations. J Pers 2001;69:27-55.
49. Branje SJ, Van Lieshout CF, Van Aken MA. Relations between Big Five personality characteristics and perceived support in adolescents' families. J Pers Soc Psychol 2004;86:615-628.
50. Ferrell BR, Grant MM, Funk B, Otis-Green S, Garcia N. Quality of life in breast cancer survivors as identified by focus groups. Psycho-oncology 1997;6:13-23.
51. Lim JW, Zebrack B. Different pathways in social support and quality of life between Korean American and Korean breast and gynecological cancer survivors. Qual Life Res 2008;17:679-689.

Chapter 7
Clinical factors are not the best predictors of quality of sexual life and sexual functioning in women with early stage breast cancer*

* Den Oudsten BL, Van Heck GL, Van der Steeg AFW, Roukema JA, De Vries J. Clinical factors are not the best predictors of quality of sexual life and sexual functioning in women with early stage breast cancer. (Submitted for publication).

Abstract

Background: Few studies have prospectively assessed the impact of breast cancer (BC) on women's sexual lives. Therefore, this study examines the determinants of quality of sexual life (QOSL), sexual functioning (SF), and sexual enjoyment (SE) at six and 12 months after surgical treatment. *Methods:* All participants completed a measure of QOSL (WHOQOL-100-facet Sexual Activity) before diagnosis (Time-1), and one (Time-2), 3 (Time-3), 6 (Time-4) and 12 months (Time-5) after surgical treatment. At Time-1, women also completed questionnaires on personality (STAI-trait, NEO-FFI), body image and self-esteem (WHOQOL-100), depressive symptoms (CES-D), and fatigue (FAS). Furthermore, SF and SE (EORTC-QLQ-BR23) were measured from Time-2 onwards. *Results***:** At baseline, the analysis included 223 women with early stage BC. Clinical factors did not predict QOSL, SF or SE. In the final analyses, trait anxiety predicted QOSL and SF at Time-4 (*p*s<.01). At Time-5, agreeableness predicted QOSL and SE (*p*s<.05). Having a partner and age predicted SF, while SE was predicted by educational level (Time-4). In addition, fatigue predicted SE at Time-4 (*p*<.05). With regard to type of surgery, QOSL diminished across time, while SF improved. However, women with a mastectomy did not differ from women with breast conserving therapy. *Conclusions***:** Mainly personality and psychological factors affect patients' sexuality after surgical treatment. Clinical factors did not predict QOSL, SF or SE. More knowledge in this field will help professionals to identify women who are at risk of experiencing sexual problems and consequently will contribute to provide adequate support.

Introduction

In Europe, breast cancer (BC) is the predominant type of malignancy among women. Although studies have shown that about two-third of women with a partner will remain sexually active after cancer diagnosis or at the end of treatment [1-3], research also indicates that BC can negatively impact women's sexual functioning (SF) [4]. As sexuality is considered to be an important aspect of quality of life [5, 6], research is needed to better understand long-term sexual problems in order to be able to adequately provide support to women with early stage BC.

Most studies on sexuality in BC are cross-sectional [7-14]. In general, studies focus on the impact of surgical treatment [10, 13] or chemotherapy [10-12, 14] on sexual functioning (i.e., the experience of sexual difficulties) and sexual activity (i.e., the frequency of sexual activities). In addition, some studies reported on sexual satisfaction [9, 14-16].

In 1998, Ganz et al. [9] have proposed a broad conceptual model in which sexual health, encompassing sexual interest, sexual dysfunction and sexual satisfaction, were determined by sociodemographic and personal characteristics, medical variables, body image, partner relationship, and health-related quality of life. Since then, various determinants have been examined prospectively [1, 15-18]. Several clinical factors, for instance, vaginal dryness [9, 16, 17], chemotherapy [9, 18], disease stage [18], distant recurrence [15], and sexual functioning before diagnosis [16], seem to be associated with sexual problems. Furthermore, research has demonstrated that marital status [17], age [15, 18], mental health [17], and body image [17] predicts SF. Women tend to be more sexually active if they had an unmarried relationship, had two or more children at home, experienced more vitality, and reported vaginal dryness [17]. Burwell et al. [16] found no significant changes in satisfaction with sex life across time. Prospective studies examining the determinants of sexuality, however, are rather scarce. Furthermore, the fact that several related concepts have been used as endpoints makes it difficult to compare the various studies.

Few cross-sectional studies have examined the relationship between fatigue and depression, on the one hand, and sexuality, on the other hand. However, the limited body of studies has shown sizeable associations between

fatigue and depression, on the one hand, and sexuality, on the other hand [19, 20]. However, prospective data are lacking. Therefore, the associations between depressive symptoms and fatigue and QOSL, SF, and SE were examined in this longitudinal study, using a prospective design.

Besides the necessity to include control groups, recently, Fobair et al. [17] also stressed the need for longitudinal studies, examining the relationships between body image and sexual functioning, interactions between side effects of BC treatment and mental health, self-esteem, and difficulties with relationships.

In line with the Ganz et al. position that personal characteristics could play a role in sexual health, we focused in the current study on basic personality factors. Despite the known influences of personality traits on quality of life-related concepts, no extensive studies have been conducted on the role of personality in relation to quality of sexual life, SF, and sexual enjoyment. In 1992, Costa et al. [21] conducted a study incorporating personality factors. They have shown that, for instance, neuroticism was related to lowered body image and sexual functioning.

The present prospective, longitudinal study examined the determinants of the quality of sexual life (QOSL), SF, and sexual enjoyment (SE) at six and 12 months in women with early stage BC after surgical treatment. In this research, the role of sociodemographic, clinical, psychological, and personality factors were examined. Concerning personality factors, we hypothesized that trait anxiety and neuroticism would factors contributing to the prediction of QOSL, SF, and SE.

Method

Participants

Women with a palpable lump in the breast or an abnormality on a screening mammography were referred by their general practitioner to the Department of Surgery of the outpatient clinics of the St. Elisabeth Hospital (Tilburg), the Maasland Hospital (Sittard), or the Jeroen Bosch Hospital (Den Bosch) in The Netherlands. The present study is part of a larger study focusing on the role of personality in early stage BC patients' quality of life. The data were collected from September 2002 until September 2006. From the 799 eligible women, 604

(75.6%) completed the first set of questionnaires before they visited the surgeon or radiologist, i.e. before the diagnosis, benign or malignant, was known (Time-1). In this group (N = 604), 223 appeared to have early stage BC; the others had a benign breast problem (BBP).

The main reasons for not participating were the length of questionnaires and the amount of stress at the first visit at the hospital. Woman with a history of abnormalities in the breast, benign or malignant, or a breast tumor that was too large (>5 centimeter) for BCT, were excluded from the study. Participants had to be able to read and write in Dutch.

After the baseline measurement before diagnosis (Time-1), the participants were divided in two groups: women with early stage breast cancer (BC group) and women with benign breast problems (BBP group). Thereafter, women completed questionnaires at 1, (Time-2), 3 (Time-3), 6 (Time-4), and 12 (Time-5) months after diagnosis (BBP) or surgical treatment (BC). Once diagnosis was known, this was the reference point for subsequent measurement times for BBP. For BC patients, the reference point was surgical treatment. This was chosen, because otherwise the timing of treatment modalities would interfere with follow-up measures. Participation in the study was not known by the surgeon in attendance and, therefore, could not affect treatment and clinical follow-up. All participants gave written informed consent. This study was approved by the local ethical committee.

Measures

All participants completed a measurement of QOSL (WHOQOL-100-facet Sexual Activity) at all time points. At Time-1, women also completed questionnaires on personality (STAI-trait, NEO-FFI), body image and self-esteem (WHOQOL-100), depressive symptoms (CES-D), and fatigue (FAS). Furthermore, women with BC completed a disease-specific measurement (EORTC-QLQ-BR23) of SF and SE from Time-2 onwards.

The World Health Organization Quality of Life assessment instrument-100 (WHOQOL-100) [22] is a, cross-culturally developed, generic multi-dimensional QOL measure. It covers 24 specific QOL facets, assessed by 96 questions, and one General Health and Overall Quality of Life facet. Each facet is measured with four items using 5-point Likert scales. Facet scores range from 4 to

20. Reliability and validity are adequate [23-25] and sensitivity is high [26]. In the present study, three facets were used (Self-esteem, Body Image and Appearance, and Sexual Activity). Higher scores on these facets indicate good QOL. The facet Sexual Activity (α = .83) captures general satisfaction with sex life and contains the following items: 'How would you rate your sex life?', 'How well are your sexual needs fulfilled?', 'How satisfied are you with your sex life?', and 'Are you bothered by any difficulties in your sex life?'. In the general population, the mean value of this facet was 14.10 (SD = 3.93). As Sexual Activity assesses the qualitative aspects of sex life, we will use the term QOSL in the remaining text.

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer module (EORTC QLQ BR-23) [27, 28] is a supplementary module of the EORTC QLQ C30. The EORTC QLQ BR-23 incorporates two functional scales (Body Image and Sexual Functioning) and three symptom scales (Arm Symptoms, Breast Symptoms, and Systematic Therapy Side Effects). The remaining items assess sexual enjoyment and distress related to hair loss. Each item is rated on a scale ranging from 0 (*not at all*) to 4 (*very much*). All scores of the QLQ-BR23 were transformed linearly so that all scales ranged from 0 to 100. Reliability, validity and sensitivity are adequate [28, 29]. In the present study, two scales were used: Sexual Functioning and Sexual Enjoyment). Higher scores represent higher levels of functioning. The subscale Sexual Functioning (α = .88) captures interest and activity and contains the following items: 'To what extent were you interested in sex?' and 'To what extent were you sexually active?' (with or without intercourse). Sexual Enjoyment is assessed by: 'To what extent was sex enjoyable for you?'.

Basic personality factors were assessed with the Neuroticism-Extraversion-Openness-Five Factor Inventory (NEO-FFI) [30-32]. This self-report questionnaire consists of 60 statements covering the five broad dimensions of personality that formed the Five-Factor Model FFM) [33]: Neuroticism, Extraversion, Openness to New Experiences, Agreeableness, and Conscientiousness. Each statement is rated on a 5-point scale ranging from 1 (*strongly disagree*) to 5 (*strongly agree*), resulting in dimension scores between 12 and 60. The psychometrics of the NEO-FFI have been extensively examined. The internal consistency, test-retest reliability, as well as the convergent validity, are acceptable to good [32].

The State Trait Anxiety Inventory (STAI) [34, 35] consists of two 20-item scales for measuring state anxiety and trait anxiety. In the present study, only the Trait Anxiety Scale was used. This scale describes how persons generally feel. The STAI trait scale has a 4-point rating scale ranging from 1 (*almost never*) to 4 (*almost always*). The Dutch version of the STAI Trait Anxiety scale has good reliability and validity [35].

Medical records

Data concerning type of surgery (breast conserving therapy; BCT or mastectomy; MTC), disease stage, and adjuvant treatment were obtained from the medical records of the patients.

Statistical procedure

Frequencies were used to present the available sociodemographic and clinical data. Student t-tests and chi-square tests were used to examine differences between (i) participants and non-participants and (ii) the BC group and the BBP group. Sexual Functioning, Sexual Enjoyment, and Quality of Sexual Life are partially overlapping constructs. In spite of this relatedness, they should be conceived of as separate variables. Therefore, using the Time-2 scores, the intercorrelations between Sexual Functioning, Sexual Enjoyment, and Quality of Sexual Life were calculated. As a first step, aiming at minimizing the number of independent variables in the final regression analysis, separate preliminary regression analyses (method: Enter) were performed with sociodemographic (age, having children, partner status, educational level, work status), clinical (disease stage, type of surgery, chemotherapy, radiotherapy, hormone therapy), psychological (body image, self-esteem, depressive symptoms, fatigue), and personality factors (neuroticism, extraversion, agreeableness, openness to new experiences, conscientiousness, trait anxiety) as independent variables. These variables were used to predict QOSL, SF, and SE at two measurement points: Time-4 and Time-5 (BC group). Subsequently, significant predictors (p <.05) were entered in the final regression analyses (method: Enter). General linear model analysis for repeated measures was used to examine QOSL scores across time with regard to diagnosis (BC and BBP group) and trait anxiety (low/moderate versus high scores). In addition, QOSL across time was examined

with regard to BCT or MTC. Women with BBP were included as a reference group. In addition, we examined the interaction between age and type of diagnosis for the QOSL measure. Therefore, the sample was stratified by age, according to the menopausal status of these women. All analyses were performed with the Statistical Package for Social Sciences (SPSS version 14.0).

Results

Sample characteristics

In total, 799 patients were eligible for this study. Before diagnosis was known, 609 (76.2%) completed the first set of questionnaires before they visited the surgeon or radiologist. Participants were significantly younger compared with non-participants (p =.002). Participants and non-participants did not differ on other sociodemographic or clinical characteristics. A flow chart is presented in Figure 1.

At baseline, the BC group (n =223) was significantly older compared with the BBP group (n=486; p<.0001). Participants in the BC group were less often employed (p=.001). In addition, the BBP group scored higher on Neuroticism (p =.048) and Openness to New Experiences (p=.001). Concerning the remaining personality characteristics, the BBP and BC group were not statistically different (Table 1).

At baseline, 83.4% of the women with BC and 81.5% of the women with BBP reported on the QOSL-scale that they were not bothered or only a little bothered by the presence of sexual difficulties.

Figure 1. Flow chart

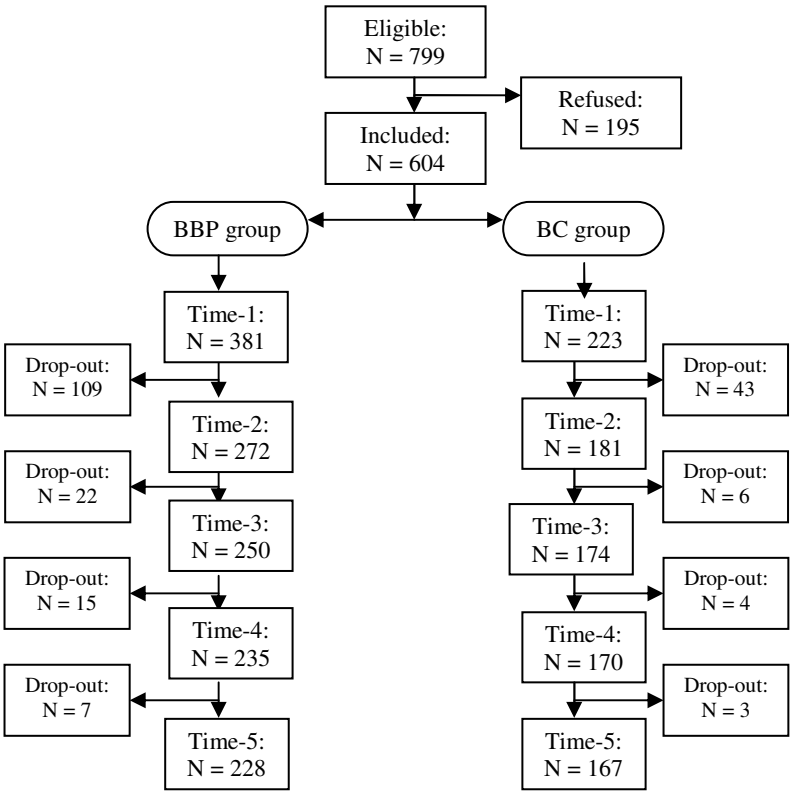


Table 1. Baseline characteristics of women with early stage BC and BBP

	BC group (n = 223)	BBP group (n = 383)	p-value
Age at diagnosis (mean ± SD; range)	58.7 ± 9.4; 34-87	52.9 ± 10.4; 19-83	<.0001
Living with a partner *(yes /no /missing)*	179 (80.3)/ 37 (16.6)/ 3 (1.3)	325 (84.9)/ 51 (13.3)/ 7 (0.6)	ns
Having children *(yes / no / missing)*	191 (85.7)/ 29 (13.0)/ 3 (1.3)	323 (84.3)/ 57 (15.9)/ 3 (0.8)	ns
Education level *0-9/ 10-14/ > 14 years/ missing*	85 (38.1)/ 95 (42.6)/ 37 (16.6) / 2 (0.9)	133 (34.7)/ 171 (44.6)/ 72 (18.8) / 4 (1.0)	ns
Paid work *(yes / no / missing)*	85 (38.1)/ 135 (60.5)/ 1 (0.4)	199 (52.0)/ 178 (46.5)/ 6 (1.6)	.001
Diameter of tumor: *< 1 cm / 1-3 cm / > 3 cm*	49 (22.0)/ 146 (65.5)/ 25 (11.2)		
Type of surgery: *BCT / MTC / No surgical treatment*	107 (48.0)/ 114 (51.1)/ 2 (0.9)		
Adjuvant therapy*:*Yes / No*	169 (75.8)/ 54 (24.2)		
Chemotherapy: *(yes / no / missing)*	60 (26.8)/ 162 (72.3) / 2 (0.9)		
Radiotherapy: *(yes / no / missing)*	117 (52.2)/ 106 (47.3)/ 1 (0.4)		
Hormone therapy: *(yes / no / missing)*	87 (38.8)/ 136 (60.7)/ 1 (0.4)		
Disease stage:			
Stage 0	24 (10.8)		
Stage I	93 (41.7)		
Stage IIa / Stage IIb	69 (30.9)/ 35 (15.7)		
Indefinable	2 (0.9)		
Neuroticism (mean ± SD)	30.2 ± 7.0	31.4 ± 7.1	.048
Extraversion (mean ± SD)	41.1 ± 5.5	40.2 ± 5.8	ns
Openness to New Experiences (mean ± SD)	35.4 ± 6.0	37.1 ± 5.8	.001
Agreeableness (mean ± SD)	43.5 ± 4.1	43.4 ± 4.4	ns
Conscientiousness (mean ± SD)	45.5 ± 5.4	45.0 ± 5.3	ns
Trait Anxiety (mean ± SD)	39.4 ± 11.0	38.8 ± 10.6	ns
Quality of Sexual Life (mean ± SD)	15.0 ± 3.1	14.9 ± 3.3	ns
Sexual Functioning (Time-2; mean ± SD)	29.5 ± 21.9		
Sexual Enjoyment (Time-2; mean ± SD)	55.7 ± 22.2		
Depressive symptoms (mean ± SD)	14.9 ± 9.5	14.6 ± 10.5	ns
Fatigue (mean ± SD)	19.8 ± 6.9	20.9 ± 7.1	ns
Self-esteem (mean ± SD)	14.8 ± 2.3	14.4 ± 2.1	.035
Body Image (mean ± SD)	16.5 ± 2.9	6.0 ± 3.3	ns

Abbreviations: BCT = Breast Conserving Therapy, MTC = Mastectomy
Note: * = more than one treatment possible.

At Time-4 and Time-5, these percentages in the BC group dropped significantly: 75.4% and 71% (p<.0001), respectively. About 10% of the women with BC and BBP rated their sex life as bad or pretty bad. These percentages remained stable across time. A minority of the women is initially very unsatisfied or unsatisfied with their sex life.

However, these percentages significantly rise in the group of women with BC, 4.3% (at baseline), 11% (Time-4), and 11.4% (Time-5; p<.0001). About a quarter of the women with BC and 18.4% of the women with BBP felt that their sexual needs were not or almost not fulfilled at Time-5 (p>.05).

Predictors of sexual health

Correlation coefficients between the subscales assessing SF, SE, and QOSL ranged from .49 (QOSL and SE) to .57 (SE and SF; p<.0001; 2-tailed).

Preliminary linear regression analyses (Table 2 to Table 4) revealed that none of the clinical factors predicted QOSL, SF, or SE. Thus, type of surgery or adjuvant therapy did not substantially contribute to the prediction of QOSL, SF or SE. Therefore, clinical factors were not entered in the final analyses. Regarding QOSL, Trait-Anxiety (ß=-.30) and Extraversion (ß=.21) predicted QOSL at Time-4. QOSL at Time-1 was a predictor of QOSL measured at Time-4 (ß=.65) and Time-5 (ß=.62). Other psychological factors did not play a substantial role. With regard to SF, Age (ß=-.25) predicted SF at Time-5. Partner Status predicted SF at Time-5 (ß=.27). Trait-Anxiety (ß=-.21) predicted SF at Time-4. Regarding SE, Agreeableness (ß=.28) predicted SE at Time-5. Fatigue (ß=-.34) was negatively associated with SE at Time-4.

Table 2. Beta weights for preliminary multivariate analyses of Quality of Sexual Life (QOSL) after surgical treatment

Predictors	Time-4		Time-5	
	Beta	p-value	Beta	p-value
Age	-.07	.49	-.86	.47
Children	-.09	.31	-.13	.15
Partner status	.21	.02	.23	.02
Education	.00	1.00	.05	.58
Work status	.02	.86	-.05	.66
Adjusted multiple R	.03		.03	
F-value	1.77	.12	1.83	.11
Disease stage	.07	.53	.01	.94
Type of surgery	.03	.85	.16	.26
Chemotherapy	-.05	.66	-.08	.52
Radiotherapy	-.03	.84	.03	.83
Hormone therapy	-.10	.35	-.02	.88
Adjusted multiple R	-.03		-.02	
F-value	.30	.91	.53	.75
QOSL (Time-1)	.65	.000	.62	.000
Body Image	-.04	.55	-.05	.51
Self-Esteem	-.12	.15	-.03	.72
Depressive symptoms	-.14	.10	-.03	.76
Fatigue	-.09	.31	-.05	.63
Adjusted multiple R	.47		.37	
F-value	25.28	<.0001	15.69	<.0001
Neuroticism	-.07	.53	-.14	.22
Extraversion	.21	.03	.12	.25
Agreeableness	.17	.06	-.26	.005
Openness to New Exp.	-.12	.16	-.05	.573
Conscientiousness	-.06	.54	-.15	.124
Trait Anxiety	-.30	.003	-.16	.131
Adjusted multiple R	.20		.15	
F-value	6.63	<.0001	4.45	<.0001

Table 3. Beta weights for preliminary multivariate analyses of Sexual functioning (SF) after surgical treatment

Predictors	Time-4		Time-5	
	Beta	p-value	Beta	p-value
Age	-.12	.25	-.25	.02
Children	-.12	.15	.09	.29
Partner status	.24	.01	.27	.003
Education	-.11	.22	-.08	.35
Work status	.03	.81	-.04	.72
Adjusted multiple R	.07		.15	
F-value	3.06	.02	5.32	<.0001
Disease stage	.08	.52	-.03	.83
Type of surgery	.09	.53	.04	.81
Chemotherapy	-.13	.26	.07	.56
Radiotherapy	.12	.39	.11	.46
Hormone therapy	-.11	.31	-.05	.66
Adjusted multiple R	-.01		-.03	
F-value	.66	.66	.33	.89
Body Image	-.05	.65	-.01	.93
Self-Esteem	-.03	.76	.13	.29
Depressive symptoms	.10	.41	.03	.81
Fatigue	-.19	.11	-.09	.47
Adjusted multiple R	.03		-.01	
F-value	1.92	.11	.83	.51
Neuroticism	-.12	.31	-.07	.56
Extraversion	.15	.15	.14	.20
Agreeableness	.06	.51	.05	.63
Openness to New Exp.	.03	.75	.03	.76
Conscientiousness	-.03	.74	-.19	.09
Trait Anxiety	-.21	.05	-.17	.13
Adjusted multiple R	.11		.04	
F-value	3.52	.003	1.81	.10

Table 4. Beta weights for preliminary multivariate analyses of Sexual Enjoyment (SE) after surgical treatment

Predictors	Time-4		Time-5	
	Beta	p-value	Beta	p-value
Age	-.16	.28	-.12	.43
Children	-.13	.29	-.04	.76
Partner status	.05	.68	.20	.13
Education	.12	.34	.08	.51
Work status	-.01	.98	-.19	.21
Adjusted multiple R	-.01		-.01	
F-value	.82	.54	.89	.49
Disease stage	.15	.36	.05	.75
Type of surgery	-.01	.94	.09	.64
Chemotherapy	-.05	.77	-.18	.26
Radiotherapy	.12	.54	.10	.62
Hormone therapy	-.15	.29	-.10	.51
Adjusted multiple R	-.03		-.04	
F-value	.55	.73	.50	.78
Body Image	-.16	.24	.01	.92
Self-Esteem	.04	.80	-.07	.67
Depressive symptoms	.06	.72	.01	.95
Fatigue	-.34	.03	-.28	.08
Adjusted multiple R	.05		.01	
F-value	1.99	.11	1.16	.33
Neuroticism	-.05	.74	-.07	.65
Extraversion	-.01	.95	.09	.54
Agreeableness	.06	.65	.28	.04
Openness to New Exp.	-.08	.51	.02	.86
Conscientiousness	-.04	.80	-.08	.55
Trait Anxiety	-.20	.19	-.06	.71
Adjusted multiple R	-.03		.04	
F-value	.69	.66	1.51	.19

The results of the final multivariate regression analyses are shown in Table 5. QOSL at Time-1 was the strongest predictor of QOSL at Time-4 and Time-5. Trait-Anxiety and Extraversion predicted QOSL at Time-4, while at Time-5 Agreeableness contributed significantly to the prediction of QOSL. QOSL was not predicted by any of the sociodemographic factors. SF was predicted by Partner Status (Time-4 and Time-5) and Age (Time-5). Trait-Anxiety predicted SF at Time-4. Regarding SE, Fatigue was a predictor at Time-4. Agreeableness (Time-5) contributed to the prediction of SE.

The significant predictors in QOSL (Adjusted R^2 >.42) explained more variance compared with SF (Adjusted R^2 >.10) and SE models (Adjusted R^2 >.07).

Table 5. Beta weights for the final multivariate regression analyses of QOSL, SF, and SE after surgical treatment

Dependent variable	Predictors	Time-4	p-value	Time-5	p-value
QOSL	Partner (Time-1)	.07	ns	.08	Ns
	QOSL (Time-1)	.57	***	.56	***
	Trait anxiety (Time-1)	-.15	*	-	
	Agreeableness (Time-1)	-		.21	**
	Extraversion (Time-1)	.11	ns	-	
	Adjusted multiple R	.48		.42	
	F-value	32.77	***	30.22	***
SF	Age (Time-1)	-		-.23	**
	Partner (Time-1)	-		.30	**
	Trait anxiety (Time-1)	-.33	***	-	
	Adjusted multiple R	.10		.16	
	F-value	15.32	***	12.26	***
SE	Fatigue (Time-1)	-.28	*	-	
	Agreeableness (Time-1)	-		.33	**
	Adjusted multiple R	.07		.09	
	F-value	6.20	*	8.04	**

Abbreviations: QOSL = Quality of Sexual Life; SF = Sexual Functioning; SE = Sexual Enjoyment.

Note: *** = p<.0001; ** = p < .001; * = p < .05; ns = not significant; - = not in the final analysis

Trends across time

Regarding the influence of Trait-Anxiety on QOSL across time, no main effect for Time was found. However, a significant interaction effect was found (Wilks' Lambda=.89; $F(12,558)= 2.18$, $p=.012$; partial eta squared=.04; Figure 1). This indicates that QOSL scores varied accordingly to the diagnosis (BC or BBP) and scores on Trait-Anxiety (high versus low/moderate). Women with BC reported less QOSL across time independent of their score on Trait-Anxiety, while women with BBP showed an improvement on QOSL scores across time. High-scorers on Trait-Anxiety had lower scores on QOSL across all time points, irrespective of their diagnosis (BBP or BC), compared to women with low or moderate scores. Women in the BBP group (scoring low or moderately on Trait-Anxiety) scored higher on QOSL than women in the BC group at Time-5 ($t(203)=2.01$, $p=.046$). When the group was stratified according to age, fitting the menopausal status, no significant interaction effect was found between age and type of diagnosis.

Also the influence of type of surgery on QOSL across time was examined. A significant effect for Time was found (Wilks' Lambda=.783; $F(4,96)=6.653$, $p<.0001$, partial eta squared=.217; Figure 2). QOSL decreased across time. Mean scores on Time-1 (15.21 ± 3.10) significantly differed from Time-2 (14.40 ± 3.27; $p=.043$), Time-3 (14.17 ± 3.41; $p=<.0001$), Time-4 (14.03 ± 3.17; $p<.0001$), and Time-5 (14.08 ± 3.47; $p=.002$). On average, women with BCT scored lower on QOSL compared with MTC. However, these differences were at no measurement point significant. No interaction effect was found.

With regard to SF, a significant effect for Time was found (Wilks' Lambda=.88; $F(3,80) = 3.63$, $p=.016$; partial eta squared =.12; Figure 3). Women tend to show an increase in SF across time. Post hoc tests indicated that mean scores on Time-2 (26.19 ± 20.58) were statistically different from Time-5 (30.36 ± 21.82; $p=.038$). Women with MTC had higher SF-scores compared with women with BTC at all time points, except for Time-3. However, differences were at no point significant. No interaction effect was found.

Figure 2. Mean scores on QOSL across time for women with BBP and BC. Women were divided in four groups according to diagnosis (benign or breast cancer) and trait anxiety (low / moderately or high).

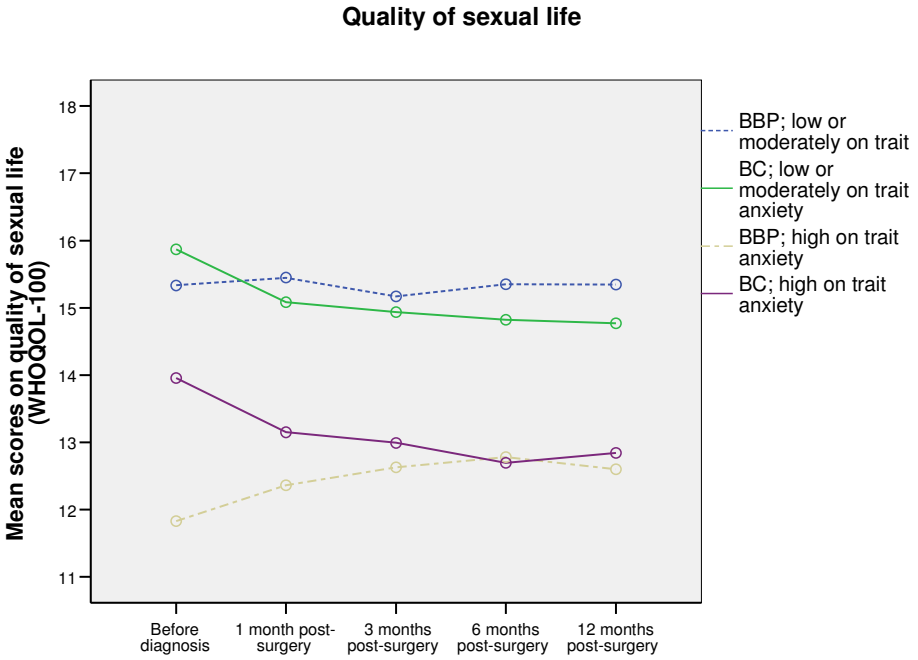


Figure 3. Mean scores on QOSL across time for women with BCT and MTC. Higher mean scores indicate higher levels of satisfaction.

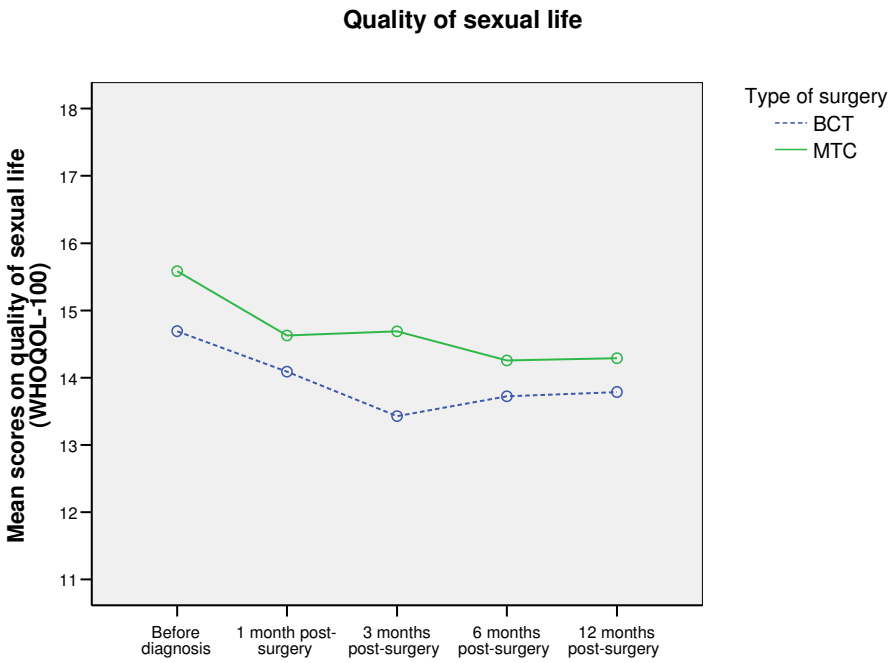
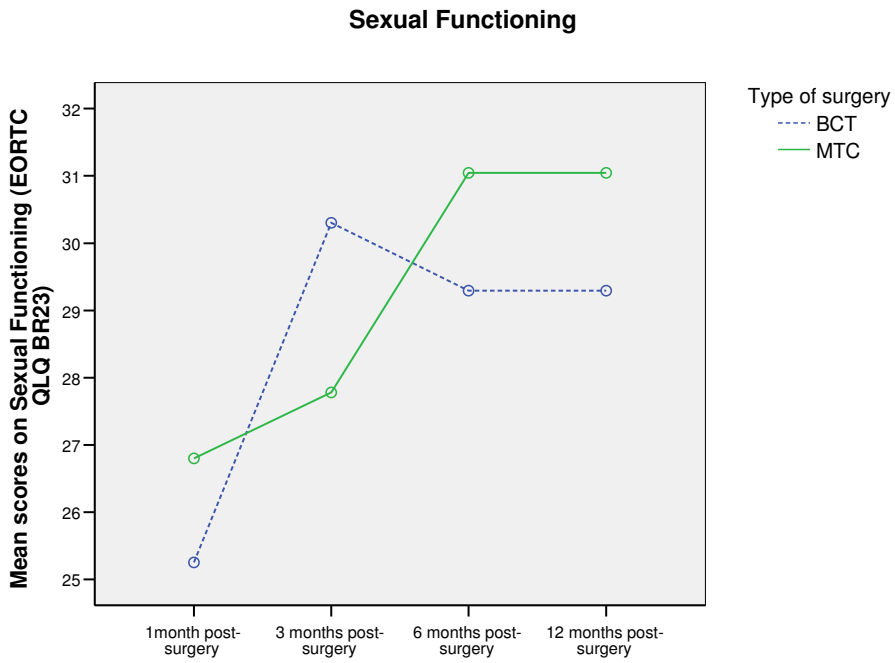


Figure 4. Mean scores on SF across time for women with BCT and MTC. Higher mean scores indicate higher levels of SF.



Discussion

The aim of this prospective study was to examine the determinants of QOSL, SF, and SE in women with early stage BC at six and 12 months after surgical treatment. This study adds to the common knowledge information about sexuality before diagnosis, it compares sexual issues of women with early stage BC with women with BBP. Furthermore, this study employs a broad view on sexuality by describing distinct but also related concepts, i.e. QOSL, SF, and SE. To the best of our knowledge, this is the first prospective study examining the role of personality in sexuality in women with early stage BC.

The QOSL model explained at least 42% of the variance, with the common significant predictors: QOSL before diagnosis and personality characteristics. QOSL before diagnosis was a significant predictor of QOSL at both time points. It is assumed that QOSL is related to the quality of the partnered

relationship. It seems that QOSL before diagnosis is buffering for QOSL after surgical treatment. As such, this finding is consistent with Ganz et al. [9]. Trait-Anxiety was a predictor of QOSL at Time-4, while Agreeableness (i.e., the inclination towards interpersonal trust and consideration of others) predicted QOSL at Time-5. The period after surgical treatment is a very dynamic one, in which women are confronted with various taxing adaptational tasks. Consequently, it is understandable that different personality factors play a prominent role at different time points. For instance, it is quite conceivable that in the period around surgical treatment anxiety would contribute more to outcome, while the role of agreeableness would be more substantial in the long-term. However, this explanation does not do justice to the complexity of the interplay between personality and situation. Consistent with findings from other studies: QOSL, SF or SE were not related to type of surgery [9, 36] or body image [16]. However, other studies found that chemotherapy was related to greater sexual problems [9, 14] early after surgery and beyond the first year after treatment [16].

In conclusion, we could demonstrate that mainly personality and psychological factors were predictors of QOSL and SE. In addition, we found that different factors predicted QOSL, SF, and SE scores at Time-4 and Time-5. Consistent with other studies, QOSL and SF were quite stable during the first year when women were compared in terms of type of surgery. Burwell et al. [16] found that women experienced considerably more sexual problems in various MOS Sexual Functioning-domains, i.e., Interest and Arousal, compared with MOS Sexual Functioning-scores after surgery, which is consistent with our results. We also found that the number of women in the BC group who were not or just a little bothered by sexual difficulties decreased compared with scores before diagnosis.

This study has some limitations. The current sample consists of a relatively homogeneous sample, in which only women with early stage BC are included, which limits generalizability. It was not possible to include levels of SF and SE before the diagnosis was known. Several studies included information on the presence of menopause resulting from adjuvant therapy [17], or included specific physical problems (e.g., vaginal dryness) women experienced. We did not assess these aspects. It is likely that they would be good predictors of SF.

Future prospective studies should include a broad range of predictors in order to fully understand the determinants of sexual health. In addition, investigations should have a follow-up period longer than 12 months. Furthermore, wide-ranging concepts should be used in order to assess sexual health. Several studies have examined to what extent women remain sexually active, the frequency of sexual intercourse or specific physical problems women experience during sexual intercourse. Although these assessments are relevant, it may also be important to include measures that focus on relevant subjective experiences. Although this study did find that clinical factors were less relevant than other constructs, future studies are still needed to draw more definite conclusions, especially, because our study did not include, for instance, current treatment status, co-morbidity, menopausal status, and vaginal dryness. In addition, studies have not included the partners' view of the sexual relationship. The inclusion of this kind of information could shed more light on the interaction between partners. Now, assessments are solely based on the experiences of the women with early stage BC and are, therefore, unilateral.

Understanding specific aspects of QOSL and SF that affect women with breast cancer across time is relevant for oncologists, nurse practitioners, and medical psychologists. For instance, when women are diagnosed with BC, women should be informed about the possible consequences with respect to sexual health and body image. Discussing sexual issues with women with BC is of utmost importance. However, a majority of health professionals find it difficult to discuss the subject. Therefore, it is important that they are aware of the problems experienced in this patient group. In this way, they could normalize problems that are the result of diagnosis and subsequent treatment of BC.

In summary, the findings from this study indicate that mainly personality and psychological factors have an impact on patients' sexuality after surgical treatment. Clinical factors, even type of surgery, did not contribute substantially to the prediction of QOSL, SF, or SE. More knowledge about the experiences of women with BC with regard to sexuality will help professionals to identify women who are at risk of experiencing sexual problems and to support them adequately. Knowledge in this field will help clinicians realize the impact of cancer on sexuality.

References

1. Bloom JR, Stewart SL, Chang S, Banks PJ. Then and now: quality of life of young breast cancer survivors. Psycho-oncology 2004;13:147-160.
2. Ganz PA, Kwan L, Stanton AL, Krupnick JL, Rowland JH, Meyerowitz BE, et al. Quality of life at the end of primary treatment of breast cancer: first results from the moving beyond cancer randomized trial. J Natl Cancer Inst 2004;96:376-387.
3. Berglund G, Nystedt M, Bolund C, Sjoden PO, Rutquist LE. Effect of endocrine treatment on sexuality in premenopausal breast cancer patients: a prospective randomized study. J Clin Oncol 2001;19:2788-2796.
4. Thors CL, Broeckel JA, Jacobsen PB. Sexual functioning in breast cancer survivors. Cancer Control 2001;8:442-448.
5. Katz A. The sounds of silence: sexuality information for cancer patients. J Clin Oncol 2005;23:238-241.
6. Avis NE, Crawford S, Manuel J. Quality of life among younger women with breast cancer. J Clin Oncol 2005;23:3322-3330.
7. Barni S, Mondin R. Sexual dysfunction in treated breast cancer patients. Ann Oncol 1997;8:149-153.
8. Takahashi M, Ohno S, Inoue H, Kataoka A, Yamaguchi H, Uchida Y, et al. Impact of breast cancer diagnosis and treatment on women's sexuality: a survey of Japanese patients. Psycho-oncology 2008;17:901-907.
9. Ganz PA, Desmond KA, Belin TR, Meyerowitz BE, Rowland JH. Predictors of sexual health in women after a breast cancer diagnosis. J Clin Oncol 1999;17:2371-2380.
10. Ganz PA, Rowland JH, Desmond K, Meyerowitz BE, Wyatt GE. Life after breast cancer: understanding women's health-related quality of life and sexual functioning. J Clin Oncol 1998;16:501-514.
11. Broeckel JA, Thors CL, Jacobsen PB, Small M, Cox CE. Sexual functioning in long-term breast cancer survivors treated with adjuvant chemotherapy. Breast Cancer Res Treat 2002;75:241-248.
12. Malinovszky KM, Gould A, Foster E, Cameron D, Humphreys A, Crown J, et al. Quality of life and sexual function after high-dose or conventional

chemotherapy for high-risk breast cancer. Br J Cancer 2006;95:1626-1631.

13. Yurek D, Farrar W, Andersen BL. Breast cancer surgery: comparing surgical groups and determining individual differences in postoperative sexuality and body change stress. J Consult Clin Psychol 2000;68:697-709.
14. Young-McCaughan S. Sexual functioning in women with breast cancer after treatment with adjuvant therapy. Cancer Nurs 1996;19:308-319.
15. Andersen BL, Carpenter KM, Yang HC, Shapiro CL. Sexual well-being among partnered women with breast cancer recurrence. J Clin Oncol 2007;25:3151-3157.
16. Burwell SR, Case LD, Kaelin C, Avis NE. Sexual problems in younger women after breast cancer surgery. J Clin Oncol 2006;24:2815-21.
17. Fobair P, Stewart SL, Chang S, D'Onofrio C, Banks PJ, Bloom JR. Body image and sexual problems in young women with breast cancer. Psycho-oncology 2006;15:579-594.
18. Schou I, Ekeberg O, Sandvik L, Hjermstad MJ, Ruland CM. Multiple predictors of health-related quality of life in early stage breast cancer. Data from a year follow-up study compared with the general population. Qual Life Res 2005;14:1813-1823.
19. Carmack Taylor CL, Basen-Engquist K, Shinn EH, Bodurka DC. Predictors of sexual functioning in ovarian cancer patients. J Clin Oncol 2004;22:881-889.
20. Green MS, Naumann RW, Elliot M, Hall JB, Higgins RV, Grigsby JH. Sexual dysfunction following vulvectomy. Gynecol Oncol 2000;77:73-77.
21. Costa PT, Jr., Fagan PJ, Piedmont RL, Ponticas Y, Wise TN. The five-factor model of personality and sexual functioning in outpatient men and women. Psychiatr Med 1992;10:199-215.
22. WHOQOL Group. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc Sci Med 1998;46:1569-1585.

23. Power M, Harper A, Bullinger M. The World Health Organization WHOQOL-100: tests of the universality of Quality of Life in 15 different cultural groups worldwide. Health Psychol 1999;18:495-505.
24. De Vries J, Van Heck GL. The World Health Organization Quality of Life assessment instrument (WHOQOL-100): validation study with the Dutch version. Eur J Psychol Assess 1997;13:164-178.
25. Den Oudsten BL, Van Heck GL, Van der Steeg AF, Roukema JA, De Vries J. The WHOQOL-100 has good psychometric properties in breast cancer patients. J Clin Epidemiol 2009; 62:195-05.
26. O'Carroll RE, Smith K, Couston M, Cossar JA, Hayes PC. A comparison of the WHOQOL-100 and the WHOQOL-BREF in detecting change in quality of life following liver transplantation. Qual Life Res 2000;9:121-124.
27. Montazeri A, Harirchi I, Vahdani M, Khaleghi F, Jarvandi S, Ebrahimi M, et al. The EORTC breast cancer-specific quality of life questionnaire (EORTC QLQ-BR23): translation and validation study of the Iranian version. Qual Life Res 2000;9:177-184.
28. Sprangers MA, Groenvold M, Arraras JI, Franklin J, Te Velde A, Muller M, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996;14:2756-68.
29. Yun YH, Bae SH, Kang IO, Shin KH, Lee R, Kwon SI, et al. Cross-cultural application of the Korean version of the European Organization for Research and Treatment of Cancer (EORTC) Breast-Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23). Support Care Cancer 2004;12:441-445.
30. Costa PT, McCrae RR. The NEO Personality Inventory Manual. Odessa, FL: Psychological Assessment Resources Inc.; 1985.
31. Costa PT, McCrae RR. Revised NEO Personality Inventory (NEO-PI-R) and NEO Five Factor Inventory (NEO-FFI) professional manual. Odessa, FL: Psychological Assessment Resources Inc.; 1992.
32. Hoekstra H, Ormel J, De Fruyt F. Handleiding NEO persoonlijkheidsvragenlijsten NEO-PI-R en NEO-FFI [manual NEO

personality questionnaires NEO-PI-R and NEO-FFI]. Lisse, The Netherlands: Swets Test Services; 1996.

33. McCrae RR, John OP. An introduction to the five-factor model and its applications. J Pers 1992;60:175-215.
34. Spielberger CD, Gorsuch RL, Lushene RE. STAI manual for the State-Trait Anxiety Inventory. Palo-Alto, CA: Consulting Psychologists Press; 1970.
35. Van der Ploeg HM, Defares PB, Spielberger CD. ZBV: a Dutch-language adaptation of the Spielberger State-Trait Anxiety Inventory. Lisse, The Netherlands: Swets & Zeitlinger; 1980.
36. Ganz PA, Schag AC, Lee JJ, Polinsky ML, Tan SJ. Breast conservation versus mastectomy. Is there a difference in psychological adjustment or quality of life in the year after surgery? Cancer 1992;69:1729-1738.

Chapter 8
General discussion and clinical implications

The aim of this thesis was to examine the psychosocial outcomes of women with early stage BC in a longitudinal follow-up study. In the first part of this chapter, the main findings of the separate studies are summarized. Subsequently, potential implications of the findings for clinical practice are discussed. Finally, some general methodological considerations combined with recommendations for future research are made.

Main findings

Quality of life in women with early stage BC

The majority of earlier studies have examined health status (HS) instead of the broader concept quality of life (QOL). Although the debate on conceptualisation of patient-centred outcomes is not settled yet, the focus of the first part of the thesis (Part A) was to shift focus from functioning or, in other words, what persons can or cannot do in their daily life, to the evaluation of patients of their functioning [1]. Currently, only a few questionnaires are developed in such a way that they focus on QOL, i.e., instruments that are focussing on the individual's subjective perception.

In this thesis, the main focus was on QOL. The WHOQOL instruments are generic and cross-culturally developed questionnaires and assess QOL. The WHOQOL-100 was not tested psychometrically in breast cancer patients. Therefore, the aim of chapter 2 was to examine the psychometric properties of the WHOQOL-100 in this particular population. Results showed that the WHOQOL-100 can be effectively used in women with early stage breast cancer (BC). In chapter 3, the objective was to examine which QOL domains and facets contributed most to patients' overall QOL during the first year after surgical treatment. Different facets contributed to overall QOL over time. However, the consistently predominant contributors to overall QOL during the first year after surgical treatment were scores on Positive Feelings, reflecting the amount of happiness and enjoyment in life, and scores on Personal Relationship, reflecting satisfaction with relationships with family and friends.

Psychological outcomes

In the literature on depressive symptoms, various risk factors have been examined. However, previous studies differ substantially with regard to their study design, sample size, concepts assessed, and populations examined, as well as factors under consideration. Due to these discrepancies, there are striking inconsistencies regarding the role of biopsychosocial factors and their association with depressive symptoms. Former studies that focused on rather limited sets of predictors found that depression has a detrimental impact on patients' lives [2-4], adversely affects compliance with medical treatment [5], significantly influences recovery from treatment [6], and may reduce survival length [7-9]. In addition, women with depression experience more side-effects of treatment [10]. Consequently, there is a need for studies examining a broad range of factors reflecting socio-demographic, clinical, social as well as psychological variables, including personality traits. Chapter 4 focused on such a broad range of predictors of depressive symptoms 12 months after surgical treatment. Depressive symptoms at 12 months after surgical treatment were predicted by lower scores on agreeableness (i.e., a tendency to be compassionate and cooperative rather than suspicious and antagonistic towards others), higher scores on neuroticism (i.e., the tendency to experience negative emotions, such as anger, anxiety, or depression), depressive symptoms at Time-1, fatigue at Time-1, and type of surgery (breast conserving therapy; BCT).

Recent studies have shown that clinical factors predict whether women receive a re-excision after BCT [11-15]. Few studies have examined the consequences of a second surgery [16]. Re-excisions may negatively affect aesthetic outcomes, and subsequently affect QOL [16, 17]. Recently, it was found that the risk of local recurrence progressively increases with the number of re-excisions required to obtain clear margins. However, to what extent additional surgical treatment is negatively affecting women with early stage BC has not been studied yet. Therefore, the aim of chapter 5 was to examine the relationship between the number of surgical treatments and psychosocial outcomes (i.e., state anxiety, fatigue, depressive symptoms, and aspects of QOL). We did not find differences between women who had one operation, compared with women who had additional surgical treatment. Initially, scores on the outcome measures did

improve over time. However, after controlling for clinical factors, only anxiety scores significantly improved over time.

Social outcomes

There is still a limited body of knowledge regarding the question whether, in line with a decreasing social network, perceived social support also diminishes across time, and what role personality plays in this relationship. Therefore, in chapter 6 the role of personality factors was examined in the relationship between stress (i.e., being diagnosed with early stage BC) and QOL. Results showed that agreeableness was positively associated with perceived social support at 12 and 24 months after diagnosis or surgical treatment, while trait anxiety (i.e., the tendency to respond to situations perceived as threatening with a rise in anxiety intensity) was negatively associated. Besides personality factors, fatigue and having a job substantially influenced the way women with early stage BC perceive social support. Having a job was negatively associated with perceived social support at two years after surgical treatment.

Sexuality is also part of the social domain. The number of studies reporting on sexual issues in women with early stage BC is rather scarce. Most studies are cross-sectional and focus on the extent in which women remain sexually active, the frequency of sexual intercourse, or specific physical problems women experience during sexual intercourse in relation to treatment. However, it may also be important to include measures that focus on the subjective experiences of these women. Therefore, the objective of chapter 7 was to examine quality of sexual life (QOSL), sexual functioning (SF), and sexual enjoyment (SE) after diagnosis and surgical treatment. This study adds to the common knowledge information about sexuality before diagnosis, it compares sexual issues of women with early stage BC with women with BBP. Furthermore, this study employs a broad view on sexuality by describing distinct but also related concepts, i.e. QOSL, SF, and SE. Personality was related to QOSL at 6 and 12 months after surgical treatment. Trait anxiety predicted QOSL at 6 months after treatment and agreeableness predicted QOSL at 12 months after treatment. Consistent with findings from other studies were the following outcomes: QOSL, SF or SE were not related to type of surgery [18, 19] or body image [20]. However, other studies found that chemotherapy was related to greater sexual

problems early after surgery [19, 21] and beyond the first year after treatment [20]. The findings from the present study indicate that mainly personality and psychological factors have an impact on patients' sexuality after surgical treatment. Clinical factors, even type of surgery, did not contribute substantially to the prediction of QOSL, SF, or SE.

Methodological considerations

Weaknesses of the current study

The work presented in this thesis has a number of limitations. First, the current study consisted of a rather homogeneous group of women with early stage BC (T1 and T2 stage). It may be that women with a more advanced cancer (T3 and T4 stage) would experience a greater threat to survival [22] and, therefore, would experience more psychosocial problems. As advanced BC was not present in this sample, our results may not be generalised to that particular population, to cancer in general, or to women with recurrent breast cancer. In addition, the population of older women with BC (75+ years) is rapidly growing. However, few studies have examined the specific psychosocial problems these women are facing. In this study, we have decided to study a population with a clear therapeutic plan. As a consequence, we did not focus on this population, since therapy in older women varies. However, in the future this group will be an important target population. Second, studies like the current one often show relatively high attrition [23]. Our study had 63.7% of the women with early stage BC in the study at one-year after surgical treatment. This may have influenced our results. However, in general, women with BC who dropped out of the study did not differ from women remaining in the study, except for age. Women remaining in the study were significantly younger. The opposite was found for women with benign breast problems. Third, the sample size at one-year after diagnosis or surgical treatment was relatively small in analyses where all assessment points were used (i.e., repeated measures). This may also affect our results. It is not clear why women missed the assessment on a particular time point or why women dropped out from the study. Fourth, this study reported on self-reported outcomes, for instance, depressive symptoms. It would be interesting to combine self-reported outcomes with clinical interviews. Finally, some important factors, for instance, co-

morbidity, menopausal status, specific symptoms (i.e., vaginal dryness), and information whether any of the women had received treatment for mental health problems, have not been included. Future studies on early stage BC should further address these issues. Therefore, the results should be interpreted with caution and replication is desirable.

Strengths of the current study

Despite these limitations, the work presented in this thesis has a number of strengths. Most studies of cancer patients examined psychological status at one time point [2], whereas our findings are based on prospective longitudinal follow-up research. Moreover, this study included a baseline assessment, i.e., an assessment before diagnosis was known. This baseline assessment was used as reference point in most studies reported in this thesis. Strength is furthermore that women with benign breast problems were also included. Women with benign breast problems were included as a control group in several studies in this thesis, for instance, in the chapter on quality of sexual life, sexual functioning, and sexual enjoyment (Chapter 7). Finally, the data was collected in several hospitals, which may improve generalisability of the results.

Implications for clinical practice and future research

Understanding the specific aspects of psychosocial outcomes in women with early stage BC is relevant for oncologists, nurse practitioners, and medical psychologists. For instance, when women are diagnosed with BC, women should be informed about the possible physical and psychological consequences this disease or treatment may have.

QOL is an important concept, since it can inform surgeons and patients in the decision-making process of determining which treatment options to use. Following the results of the first part of the thesis, the WHOQOL-100 is suitable for use in women with breast problems (Chapter 2). The WHOQOL-100 can be used in clinical practice to assess subjectively experienced QOL or can be used for research purposes to determine the QOL of this population. Since our study did not examine the sensitivity and specificity of the WHOQOL-100, future studies could address this issue. Chapter 3 adds knowledge to our understanding of which factors determine the overall QOL scores of women with early stage

BC. Knowledge about these factors will allow health professionals to further adjust follow-up management to the needs of women with early stage BC. Our results showed that women may benefit from a more multidisciplinary treatment: not only focussing on the medical aspects, but also discussing the psychological, social, and environmental aspects of BC [24]. Methodologically, our findings showed that assessment instruments, which use a composite score, have an important drawback, i.e. important information about the different factors related to QOL over time is lost when composite scores are used.

In the second part of this thesis, the focus was on addressing psychological problems in women with early stage breast cancer. In chapter 4, predictors of depressive symptoms one year after surgical treatment were examined. The current study showed that some patients have an increased risk of developing depressive symptoms. Since, depression has a detrimental impact on patients' lives [2-4], it adversely affects compliance with medical treatment [5], significantly influences recovery from treatment [6], and may reduce survival length [7-9]. In addition, due to the fact that women with depression experience more side-effects of treatment [10], identification of women with depressive symptoms is particularly important. As a consequence, BC patients should be evaluated for the presence of depressive symptoms. The CES-D is easy to administer to screen for depressive symptoms and has well established cut-off values. In this study, we have shown that certain personality factors may have a profound impact on levels of functioning and/or well-being of women with early stage BC. Therefore, it seems appropriate to screen women on personality factors at the start of the diagnostic process. In this study, we used the NEO-FFI and STAI-Trait to assess personality. Although the NEO-FFI contains 60 items, it seems feasible that women complete these questionnaires once at the start of the diagnostic process. In clinical practice, screening may ideally be part of the care process. Screening could be done by nurse practitioners or other health professionals. Women who are at risk for developing depressive symptoms could be monitored more closely. The need for screening is supported by the National Program Cancer Control [Nationaal Programma Kankerbestrijding]. Currently, guidelines are developed for the detection of psychosocial problems. Although it is not clear whether women with, for instance, high scores on neuroticism tend to have a negative way of perceiving their situation or whether their situation is

worse compared with low-scorers, it is important to take into account that there is an association with their functioning. In chapter 5, the relationship between second surgery and psychological outcomes (i.e., state anxiety, fatigue, depressive symptoms, and aspects of QOL were examined. This study showed that, in general, women who had one operation did not differ from women who had a second operation. After controlling for clinical factors, only anxiety scores significantly improved over time. This study contributes to the debate whether women who receive a second surgery are at a disadvantage compared with women who are 'effectively' treated. The group of women who received a second surgery was a rather heterogeneous group. Women may receive a second surgery when the margin of tissue around the tumor is not cancer-free or when complications occur. In addition, women differed in the treatment they had received. Some women received BCT twice or women were converted from BCT to MTC. Given the relatively small sample size, it was not possible to divide the sample and examine whether differences exists between the different subgroups. It would be interesting for future studies to further address this issue.

In the final part of this thesis, we have addressed the social aspects of QOL. The aim of chapter 6 was to examine the relationships between personality and perceived availability of social support (PASS) and satisfaction with received social support (SRSS) in early stage BC patients. In addition, the role of PASS and/or SRSS was examined in the link between diagnosis and QOL. As social support is related to QOL, it seems important to discuss this issue with patients and their family. Awareness of what patients need during and after treatment could guide significant others to provide the care needed. In Chapter 7, the quality of sexual life and sexual functioning of women with early stage BC and benign breast problems were examined. Due to the sensitive nature of this topic, many patients are reluctant to discuss sexual difficulties with health professionals or to seek help for their problems. This sensitivity should also be acknowledged in the group of health professionals who may also find it difficult to discuss this subject. Partly due to this sensitivity, this topic has not yet received considerable attention by both health professionals and researchers. However, our study has shown that it is import to discuss sexual issues with these women, because one quarter of our sample was bothered by the presence of sexual difficulties at 6 and 12 months after surgical treatment. First, by studying this topic and subsequently informing

both health professionals and patients, we make them aware of the problems that may be experienced. They can address the sexual concerns by integrating them into routine clinical practice information about the areas of sexual functioning that may be impaired by treatment. This can normalize the discussion of sexual issues for health professionals, as well as the patient and his or her partner. Furthermore, health professionals can use these data to provide reassurance to their patients that the majority of women treated for BC do quite well following the completion of their treatment. Second, more knowledge about the experiences of women with BC with regard to sexuality will help professionals to identify women who are at risk of experiencing sexual problems and to support them more adequately.

References

1. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol Med 1998;28:551-558.
2. Deshields T, Tibbs T, Fan MY, Taylor M. Differences in patterns of depression after treatment for breast cancer. Psycho-oncology 2006;15:398-406.
3. Visser MR, Smets EM. Fatigue, depression and quality of life in cancer patients: how are they related? Support Care Cancer 1998;6:101-108.
4. Badger TA, Braden CJ, Mishel MH, Longman A. Depression burden, psychological adjustment, and quality of life in women with breast cancer: patterns over time. Res Nurs Health 2004;27:19-28.
5. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000;160:2101-2107.
6. Walker LG, Heys SD, Walker MB, Ogston K, Miller ID, Hutcheon AW, et al. Psychological factors can predict the response to primary chemotherapy in patients with locally advanced breast cancer. Eur J Cancer 1999;35:1783-1788.
7. Hjerl K, Andersen EW, Keiding N, Mouridsen HT, Mortensen PB, Jorgensen T. Depression as a prognostic factor for breast cancer mortality. Psychosomatics 2003;44:24-30.
8. Watson M, Haviland JS, Greer S, Davidson J, Bliss JM. Influence of psychological response on survival in breast cancer: a population-based cohort study. Lancet 1999;354:1331-1336.
9. Weihs KL, Enright TM, Simmens SJ, Reiss D. Negative affectivity, restriction of emotions, and site of metastases predict mortality in recurrent breast cancer. J Psychosom Res 2000;49:59-68.
10. Badger TA, Braden CJ, Mishel MH. Depression burden, self-help interventions, and side effect experience in women receiving treatment to breast cancer. Oncol Nurs Forum 2001;28:567-574.

11. Bani MR, Lux MP, Heusinger K, Wenkel E, Magener A, Schulz-Wendtland R, et al. Factors correlating with reexcision after breast-conserving therapy. Eur J Surg Oncol 2009;35:32-37.
12. Keskek M, Kothari M, Ardehali B, Betambeau N, Nasiri N, Gui GP. Factors predisposing to cavity margin positivity following conservation surgery for breast cancer. Eur J Surg Oncol 2004;30:1058-1064.
13. Fleming FJ, Hill AD, Mc Dermott EW, O'Doherty A, O'Higgins NJ, Quinn CM. Intraoperative margin assessment and re-excision rate in breast conserving surgery. Eur J Surg Oncol 2004;30:233-237.
14. O'Sullivan MJ, Li T, Freedman G, Morrow M. The effect of multiple reexcisions on the risk of local recurrence after breast conserving surgery. Ann Surg Oncol 2007;14:3133-3140.
15. Waljee JF, Hu ES, Newman LA, Alderman AK. Predictors of re-excision among women undergoing breast-conserving surgery for cancer. Ann Surg Oncol 2008;15:1297-1303.
16. Waljee JF, Hu ES, Ubel PA, Smith DM, Newman LA, Alderman AK. Effect of esthetic outcome after breast-conserving surgery on psychosocial functioning and quality of life. J Clin Oncol 2008;26:3331-3337.
17. Waljee JF, Hu ES, Newman LA, Alderman AK. Predictors of breast asymmetry after breast-conserving operation for breast cancer. J Am Coll Surg 2008;206:274-280.
18. Ganz PA, Schag AC, Lee JJ, Polinsky ML, Tan SJ. Breast conservation versus mastectomy. Is there a difference in psychological adjustment or quality of life in the year after surgery? Cancer 1992;69:1729-1738.
19. Ganz PA, Desmond KA, Belin TR, Meyerowitz BE, Rowland JH. Predictors of sexual health in women after a breast cancer diagnosis. J Clin Oncol 1999;17:2371-2380.
20. Burwell SR, Case LD, Kaelin C, Avis NE. Sexual problems in younger women after breast cancer surgery. J Clin Oncol 2006;24:2815-2821.
21. Young-McCaughan S. Sexual functioning in women with breast cancer after treatment with adjuvant therapy. Cancer Nurs 1996;19:308-319.
22. Wong-Kim EC, Bloom JR. Depression experienced by young women newly diagnosed with breast cancer. Psycho-oncology 2005;14:564-573.

23. Arving C, Glimelius B, Brandberg Y. Four weeks of daily assessments of anxiety, depression and activity compared to a point assessment with the Hospital Anxiety and Depression Scale. Qual Life Res 2008;17:95-104.
24. Arnold R, Ranchor AV, Sanderman R, Kempen GI, Ormel J, Suurmeijer TP. The relative contribution of domains of quality of life to overall quality of life for different chronic diseases. Qual Life Res 2004;13:883-896.

Chapter 9

Nederlandse samenvatting (Summary in Dutch)

Borstkanker is de meest voorkomende kanker bij vrouwen en de voornaamste doodsoorzaak in deze groep. Geschat wordt dat één op de negen vrouwen gedurende haar leven borstkanker zal krijgen. Borstkanker komt vooral voor bij Westerse vrouwen van 50 jaar en ouder. Het aantal vrouwen dat borstkanker overleeft groeiende is, heeft de diagnose een grote invloed op het psychosociaal functioneren. In dit proefschrift zal de psychosociale invloed van borstkanker worden onderzocht.

De meeste vrouwen in ontwikkelde landen die gediagnosticeerd worden met borstkanker in het vroege stadium zullen chirurgisch worden behandeld. Er zijn twee soorten chirurgie mogelijk: (i) de borstamputatie waarbij de hele borst wordt verwijderd en (ii) de borstbesparende operatie waarbij alleen de tumor en het omringende weefsel wordt verwijderd. Deze behandeling wordt gevolgd door radiotherapie. Een borstbesparende operatie is overigens alleen mogelijk wanneer de tumor kleiner is dan 5 cm en de tumor in verhouding tot de omvang van de borst niet te groot is.

Bij beide ingrepen zal meestal onderzoek plaatsvinden naar eventuele lymfeklieruitzaaiingen. Bij voorkeur gebeurt dit met de schildwachtklier-procedure. De schildwachtklier is een lymfeklier die direct lymfeafvloed ontvangt in het gebied in de borst waar de tumor zich bevindt. Wanneer de tumor via de lymfevaten uitzaait, komen tumorcellen meestal eerst in de schildwachtklier terecht. De schildwachtklier wordt opgespoord met behulp van een licht radioactieve stof. Als blijkt dat één of meer klieren uit de oksel is aangedaan, wordt het verwijderen van alle okselklieren geadviseerd. Hier is vaak een tweede operatie voor nodig (okselklierdissectie).

Afhankelijk van de tumorgrootte, mate van differentiatie van de tumor en de aanwezigheid van metastasen, zal adjuvante behandeling (chemotherapie, hormoontherapie, radiotherapie) worden aanbevolen. Elke vorm van adjuvante behandeling kan onafhankelijk van elkaar of in combinaties worden ingezet gedurende de behandelperiode.

Het aantal prospectieve follow-up studies dat zich richt op psychosociale uitkomsten bij vrouwen met borstkanker in het vroege stadium is beperkt. Het onderzoek in deze dissertatie is een prospectief follow-up onderzoek bij vrouwen die uiteindelijk de keuze hebben tussen een borstsparende operatie en een borstamputatie. Vrouwen met een voelbare afwijking in de borst of een afwijking

op de screening-borstfoto van het bevolkingsonderzoek werden gevraagd om mee te doen aan de studie. Voordat de diagnose bekend was, vulden de deelnemende vrouwen een set vragenlijsten in. Deze set bestond uit twee persoonlijkheidsvragenlijsten (NEO-FFI, STAI-trait), alsmede vragenlijsten betreffende de aanwezigheid van depressieve symptomen (CES-D) en vermoeidheid (FAS). Daarnaast werd een vragenlijst ingevuld die kwaliteit van leven meet (WHOQOL-100). Vrouwen met de diagnose borstkanker vulden daarenboven een vragenlijst in die de ziektespecifieke gezondheidstoestand meet (EORTC QLQ BR 23). Tot twee jaar na de diagnose en behandelingen kregen de vrouwen nog verschillende sets met de bovenstaande vragenlijsten thuisgestuurd.

Kwaliteit van leven

Kwaliteit van leven is een belangrijke uitkomstmaat binnen de oncologie geworden. Het aantal onderzoeken dat pretendeert kwaliteit van leven te bestuderen, is de laatste jaren enorm gegroeid. In het eerste deel van dit proefschrift staat dit thema dan ook centraal. Echter, wanneer een kritische houding wordt aangenomen, dan kan geconcludeerd worden dat de meeste onderzoeken zich, ondanks dat ze pretenderen gericht te zijn op kwaliteit van leven, meer richten op gerelateerde concepten, zoals gezondheidstoestand. Er is om die reden een sterke behoefte aan meetinstrumenten die daadwerkelijk kwaliteit van leven meten. Een vragenlijst die de persoonlijke evaluatie van het fysieke, psychische en sociale functioneren meet, is de Wereldgezondheidsorganisatie Kwaliteit van Leven vragenlijst (WHOQOL-100). Deze cross-culturele, generieke vragenlijst is in het verleden al in diverse onderzoeken gebruikt, maar over de psychometrisch kwaliteiten in de specifieke doelgroep vrouwen met een palpabele afwijking in de borst, was nog weinig bekend. In hoofdstuk 2 werden daarom deze eigenschappen onderzocht in diverse populaties: vrouwen met borstkanker, vrouwen met benigne borstproblematiek en vrouwen die meer dan vijf jaar geleden zijn behandeld aan borstkanker. Uit deze studie bleek dat de WHOQOL-100 een betrouwbaar en valide instrument was om kwaliteit van leven in deze groepen te meten. In hoofdstuk 3 werden de relaties tussen de domeinen en facetten van kwaliteit van leven enerzijds en algemene kwaliteit van leven anderzijds onderzocht. De hypothese was dat de domeinen en facetten die belangrijk zijn voor vrouwen met borstkanker over de tijd zouden

verschillen. Deze hypothese werd bevestigd. De facetten Positieve Gevoelens en Persoonlijke Relaties bleken belangrijke factoren te zijn op bijna alle meetmomenten, terwijl andere facetten, zoals Seksuele Activiteit, op een bepaald tijdstip (een half jaar na operatie) een significante relatie had met kwaliteit van leven. Instrumenten voor het vaststellen van kwaliteit van leven kunnen somtijds aspecten van kwaliteit van leven meten die niet sterk of in het geheel niet beïnvloed worden door een bepaalde interventie. Gebruik van een samengestelde totaalscore kan dan het zicht ontnemen op wel degelijk aanwezige duidelijke effecten. De bevinding dat vooral die specifieke facetten van kwaliteit van leven, die het hebben van positieve gevoelens en het waarderen van persoonlijke relaties en seksuele activiteit weerspiegelen, van belang zijn voor vrouwen met borstkanker, onderstreept dat een gedetailleerde, meer fijnmazigere beschrijving op domein- en facetniveau in bepaalde gevallen te verkiezen is boven een globalere benadering bestaande uit het berekenen van één totaalscore voor kwaliteit van leven.

Uitkomsten op psychologisch gebied

Verschillende onderzoeken hebben aangetoond dat een meerderheid van de vrouwen die gediagnosticeerd werden met borstkanker redelijk goed omgaan met deze ziekte. Echter, er is ook een groep vrouwen die ernstige psychologische problemen ervaren, zowel direct volgend op de diagnosestelling als tijdens en na de behandeling. De emotionele consequenties van borstkanker, met name depressieve klachten, hebben relatief veel aandacht gekregen in de wetenschappelijke literatuur. De prevalentie van depressie en depressieve symptomen varieert van 1.5% tot 50%, afhankelijk van de onderzoekspopulatie, de gehanteerde definitie van depressie en de wijze waarop depressie gemeten werd. De meerderheid van de onderzoeken vond dat 20 tot 30% van de vrouwen verhoogd scoren op depressieve symptomen. Depressieve klachten lijken het meest voor te komen in de eerste 6 maanden na de diagnose. Bestaande literatuur heeft aangetoond dat socio-demografische, klinische en persoonlijkheids-kenmerken een voorspellende waarde hebben ten aanzien van depressieve klachten bij vrouwen met borstkanker. Echter, onderzoek tot nu toe heeft zich gericht op beperkte sets van factoren. In hoofdstuk 4 is daarom gekozen voor een brede aanpak. Persoonlijkheidstrekken, zoals neuroticisme en altruïsme spelen

een substantiële bij het ontwikkelen van depressieve klachten. Daarnaast speelt de emotionele gesteldheid vóór de diagnose een belangrijke rol. Vermoeidheid had eveneens een negatief effect op depressieve klachten. Tot slot werd in deze studie gevonden dat vrouwen met een borstbesparende operatie een groter risico liepen om één jaar na de operatie depressief te worden. In hoofdstuk 5 werd onderzocht in hoeverre vrouwen die een tweede operatie ondergaan meer psychosociale problemen hebben dan vrouwen die vrouwen die slechts één maal werden geopereerd. Hoewel chirurgen streven om vrouwen zo min mogelijk chirurgisch te behandelen, is dit in de praktijk niet altijd mogelijk. Sommige vrouwen hebben aanvankelijk een borstbesparende operatie ondergaan, maar als blijkt dat het weefsel rond de tumor niet vrij is van kankercellen, wordt vaak besloten om nogmaals te opereren. Tot op heden zijn er een beperkt aantal onderzoeken geweest die hebben gekeken naar welke klinische factoren bijdragen aan de noodzaak tot een heroperatie (re-excisie). Onduidelijk was of er een relatie bestaat tussen een tweede operatie en de psychologische uitkomsten. Uit onze studie bleek dat vrouwen die twee keer zijn geopereerd niet per definitie meer problemen ervaren dan vrouwen die eenmalig onder het mes zijn gegaan.

Uitkomsten op sociaal gebied

In hoofdstuk 6 stond sociale steun centraal. De relaties tussen persoonlijkheid en de mate waarin vrouwen de beschikbaarheid van sociale steun ervaren en tevreden zijn met de ontvangen steun werden onderzocht. Persoonlijkheids-kenmerken, zoals trekangst en altruïsme, speelden een rol in de mate waarin vrouwen tevreden waren met de beschikbare en verkregen steun. Hoogscoorders op trekangst en laagscoorders op altruïsme scoorden lager op ontvangen sociale steun. Ook vermoeidheid en het hebben van een baan speelde een rol bij het bepalen van de determinanten van sociale steun. Sociale steun heeft een mediërende rol in de relatie tussen een stressvolle gebeurtenis (diagnose) en kwaliteit van leven.

Verschillende onderzoeken hebben aangetoond dat borstkanker een negatieve invloed kan hebben op het seksueel functioneren van vrouwen. Ondanks dat seksualiteit wordt beschouwd als een belangrijk aspect van kwaliteit van leven, zijn er tot op heden relatief weinig studies die dit thema uitvoerig, op systematische wijze hebben onderzocht. Veel studies op dit gebied zijn cross-

sectioneel en leggen eenzijdig de nadruk op de rol van chirurgische behandeling of chemotherapie op seksueel functioneren en seksuele activiteit. Kennis ten aanzien van de kwaliteit van het seksuele leven is eveneens noodzakelijk, aangezien er een discrepantie kan bestaan tussen de aanwezigheid van seksuele problemen en hoe de persoon daarmee omgaat. In hoofdstuk 7 van dit proefschrift is het seksuele leven na behandeling onderwerp van studie geweest. Geconcludeerd werd dat vrouwen, gemiddeld genomen, in de loop van de tijd minder tevreden werden over de kwaliteit van hun seksuele leven. Persoonlijkheidskenmerken (trekangst, extraversie en altruïsme), leeftijd, het hebben van een partner en vermoeidheid beïnvloeden het seksuele leven van patiënten na behandeling.

Acknowledgement

Langs deze weg wil ik iedereen bedanken die heeft bijgedragen aan het tot stand komen van dit proefschrift.

In het bijzonder bedank ik mijn promotoren: Guus van Heck, Jolanda de Vries en Jan Anne Roukema. De afgelopen jaren heb ik enorm genoten van onze samenwerking en ben erg blij dat wij deze samenwerking voortzetten. Ik waardeer het vertrouwen dat jullie in mij hebben en de vrijheid die ik van jullie krijg in mijn werk.

De leden van de manuscriptcommissie: prof. dr. Johan Denollet, prof. dr. Hanneke de Haes, prof. dr. Maarten von Meyenfeldt, prof. dr. Robbert Sanderman en Dr. Lideke van der Steeg dank ik voor het beoordelen van dit proefschrift. Een extra woord van dank ben ik verschuldigd aan Lideke, zonder jouw medewerking had ik nu nog niet op het podium gestaan.

Rinus Verkooijen heeft mij met veel enthousiasme geholpen bij de lay-out van dit proefschrift, bedankt. Tot slot bedank ik de maker van het schilderij dat op de cover van mijn proefschrift mocht staan.

Publications

1. Den Oudsten BL, De Vries J. Quality of Life in patients with Parkinson's disease: a critical evaluation [Kwaliteit van leven bij patiënten met de ziekte van Parkinson: een kritische evaluatie]. Gedrag en Gezondheid 2006; 4: 237-253.
2. Den Oudsten BL, Van Heck GL, De Vries J. The suitability of quality of life questionnaires in the field of Parkinson's disease: a systematic review. Mov Disord 2007; 10: 1390-1401.
3. Den Oudsten BL, Van Heck GL, De Vries J. Quality of Life and related concepts in Parkinson's disease: a systematic review. Mov Disord; 2007, 11: 1528-1537.
4. Van Heck GL, Den Oudsten BL. Emotional intelligence: relationships to stress, health, and well-being. J Denollet, I Nyklíček, AJJM Vingerhoets (Eds). Emotion Regulation – conceptual and clinical issues. Springer Publishers, pp. 97-121.
5. Den Oudsten BL, Van Heck GL, Van der Steeg AFW, Roukema JA, De Vries J. The WHOQOL-100 has good psychometric properties in breast cancer patients. J Clin Epidemiol 2009; 62: 195-205.
6. Den Oudsten BL, Van Heck GL, Van der Steeg AFW, Roukema JA, De Vries J. Predictors of depressive symptoms 12 months after surgical treatment of early stage breast cancer. Psycho-oncology (*in press*).